THE MATERIALS OF LIFE

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THE MATERIALS OF LIFE

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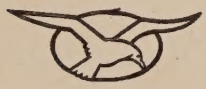
FUNDAMENTALS OF BIOCHEMISTRY

(Baltimore: Williams & Wilkins)

THE MATERIALS OF LIFE

A GENERAL PRESENTATION OF BIOCHEMISTRY

T. R. PARSONS, M.A., B.Sc.



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To Ursula

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PREFACE

MY AIM in writing this book can be stated very simply. It is to give an account that everybody shall be able to understand of the materials of which living things are made, and of the complex but fascinating changes that these materials undergo during life. The information we possess about these subjects makes up the science of biochemistry—a science that took its beginnings from the dawn of man's first intelligent curiosity as to the stuff of which he is made, that has grown through the efforts and skill of those who have devoted themselves to its study, and that, at the present time, not content with its past achievements, is reaching out to fresh conquests in a condition of flourishing development.

In order to achieve my task—in order, that is, to make my meaning clear to everyone—I have tried to employ throughout only such language as is used and understood by all of us, no matter what our previous training and experience. I have therefore not employed a single one of those complicated and at first sight terrifying formulas in which those who deal with these matters professionally are wont to express their ideas. But a chemical formula is nothing more than a concise and convenient way of representing the composition of a substance, its behaviour when it is brought into contact with other substances, the changes that it will most readily undergo and the products that it will most easily yield; and as all of this information is discovered by

direct observation and experiment and is first expressed in words long before it is ever condensed into a formula, there has seemed to me nothing essentially impossible in re-translating some of this knowledge from the cold symbolic language of technical science into the warmer, friendlier speech of everyday, in order that the inherent poetry of these things might appear.

I cannot claim to have presented in this way and in this small volume the whole of the science of biochemistry in all its intricacies and complications. Much of it is too detailed and specialised to be understood without some amount of previous technical training. But this has not deterred me from attempting to explain its general principles and more important results in such a way that the reader shall not merely be enabled to understand them but shall be stimulated to want to understand them. For this it is enough that he should be able to follow a story with interest and attention. For, after all, this science of biochemistry, like every other science, is in essence nothing but a story—the story of the adventures and discoveries of those enterprising spirits who have set out to search for the elusive answers to some of the riddles with which life is always confronting us.

T. R. PARSONS

Cambridge, England.
March, 1930.

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THE MATERIALS OF LIFE

I

THE VALUE OF BIOCHEMISTRY

To say that life is made up of a ceaseless series of changes is but to state a truism that is familiar to all. Nothing that lives can remain in exactly the same state from one moment to another; the very continuance of its life demands that it should move and feed and grow and breathe, and after each movement, each breath, each meal, although to outward appearances the organism may not show marked signs of change yet the actual materials of which its body is composed are not quite identical with those it possessed before the manifestation of these life processes. For in moving it uses up of its own substance to provide the energy required for its movement; in breathing it gives out in vaporous form materials that once constituted an intimate part of its being; and in feeding it elaborates new living matter to take the place of that that was previously lost—living stuff that must wait until in its turn it too suffers destruction that the organism as a whole may live.

The maintenance of life, then, is bound up with and dependent on this never-ceasing interplay of material—let this be interrupted for ever so short a time and at once there is lost that delicate balance between those forces of destruction and construction that are always at work in every speck of living matter, and death inevitably follows.

Now it is just this amazing simultaneous building up and breaking down of material in the bodies of living organisms that constitute the object of study of the biochemist, and it is the knowledge about these things that has been accumulated so far that makes up the science of biochemistry.

What need can there be to offer to anyone who has any taste for intellectual activity at all a reason for indulging in so fascinating a study? How can any be indifferent towards a branch of human effort that embraces knowledge not only of those changes that are unceasingly going forward in the living world around us, but of those also that take place in the depths of our own hearts? And who that delights in bringing his mental vigour to bear on difficult problems will not find herein problems of intricacy and complexity unsurpassed by any with which the human mind has ever struggled?

Here indeed have we incentive enough for interesting ourselves in these things, but even these do not by any means exhaust all the advantages that the advancement of this science can bring us. For its activities are not confined to the study of the normal healthy organism: they reach out and include the task of discovering the points in which the biochemical processes of change occurring in a sick patient differ from those taking place in a sound vigorous man, and by virtue of its manifold applications to medicine this science of biochemistry furnishes the physician with new weapons whereby he can combat disease and so bring health and vigour in place of sickness and death. The fruit that this aspect of biochemistry has so far yielded is already abundant, but we know that even now we have but touched the borders of a vast rich field of knowledge whose treasures await discovery by future searchers.

Let us illustrate our meaning by examining an example which is of such widespread importance that it has rapidly

become a matter of popular knowledge: the study of the changes that sugar undergoes in the body soon convinced biochemists that the essential disorder in the dreaded disease of diabetes is a lack of power on the part of the body to utilise sugar in a normal fashion. It was not long after that it was discovered almost accidentally that this utilisation of sugar in the normal body is dependent on the proper working of the gland known as the pancreas, and subsequent work showed that the functions of this organ are not confined to the preparation of a powerful digestive juice that passes into the intestine, but that they include the elaboration of another substance which is passed into the blood and which is absolutely essential for the proper using of sugar by the tissues. This substance is produced by certain "islands" of tissue that are scattered throughout the pancreas; for this reason it has received the name "insulin." If the pancreas be diseased insulin is not produced in sufficient amount, sugar is therefore not properly utilised by the body and the condition of diabetes supervenes. But still more recently biochemists have discovered a method of extracting insulin from the pancreas of animals slaughtered for food, so that now a diabetic patient whose own pancreas is not producing enough insulin need not be left to the lingering death which was formerly the fate of all so stricken. Thanks to biochemical science he can receive injections of the artificially extracted insulin to compensate for the deficiencies in his body's own production and can thereby be enabled to lead a life of almost normal vigour and health.

Nay—and further—the biochemist can help us not merely when the chemical mechanism of our bodies is deranged: he can also indicate ways in which health may be preserved and disease avoided. For by no means the least important part of the energies of biochemists has been devoted to a study of the foods required by the body. And as

a result of this line of investigation it has been found that not only must the body receive a sufficient quantity of such foods as yield the raw materials for replacing all that the tissues are continuously losing—this we should expect from what we have already said—but that unless there are present in the food small quantities of substances called "vitamins" very serious disturbances of health result. What these vitamins are we do not know exactly at the present time, but we do know that they are destroyed during the cooking and preserving of foods, so that they will be present in greatest abundance in fresh uncooked food; and we know further that some particular diseases are caused simply through a lack of sufficient vitamins in the food, and are cured with surprising promptness as soon as the necessary vitamins are again given. A notable case of this kind is furnished by the disease rickets, a disorder that is liable to occur in children: it produces a lack of normal development of the bones and of the teeth. We now know that this disease occurs only in such children as do not receive enough of one special vitamin in their food and that it can be stopped and cured when they are given a more satisfactory diet. Of course the disease never occurs at all in children who always receive a due amount of this vitamin. And as biochemists have made careful studies of the amounts of the various vitamins present in all kinds of foods it is easy nowadays to choose a diet that shall contain sufficient of these valuable substances for the maintenance of health.

Of course we shall have a great deal more to say about insulin and diabetes and vitamins and rickets in the later chapters of this book. We have merely mentioned these topics here as illustrations of our point that were the fascination of the subject itself not a sufficient incentive to the study of biochemistry there would be inducement enough to its vigorous

pursuit in the contributions it has already made to the welfare of mankind.

But although we have chosen human examples in order to illustrate the points we have so far made, it must not be thought that the science of biochemistry in any way restricts its attention to the study of the processes taking place in our own bodies. The chemical changes of the human body form but a small part of the complex system of changes that make up the whole scheme of animate nature. Our subject, therefore, not only deals with ourselves but includes within its scope the varied chemical changes that go on in all the various organisms with which we share the earth. The substances produced by bacteria during their lowly activities; the "fermentations" induced by such organisms as yeast; the elaboration of the host of useful materials that we obtain from ordinary green plants—these are all topics which the biochemist studies, and they all possess that double interest which we have pointed out in the changes that take place in ourselves. There is always the interest in them as subjects and problems fascinating for their own sakes together with that further interest which arises from the circumstance that we utilise these very changes in the satisfying of our elementary needs for food and clothing, in the ministration to our comfort and in the preparation of materials that assist us to combat the ills to which we are heir.

So much then for the scope of our subject. But what of the men who are devoting their lives to its study? We have already mentioned "the biochemist" a number of times and shall often have to do so again, so that it seems appropriate before we go further to stop for a moment to consider what manner of man he is. To say that he is a kind of chemist who is interested mainly in the materials composing, or derived from, living organisms will not help us much unless it is

clearly realised that by the word chemist we mean not a man who sells face powder and tooth brushes in a drug store but one who spends his days working in a laboratory full of complicated-looking apparatus by means of which he tries to find out as much as he can about the materials of which the world is made. He analyses them into their constituents; he brings different materials together and studies the kind of change that takes place when, as he says, they "react" with one another; he investigates the new products that are formed during these reactions and then in the end sits down and thinks about it all. He attempts to work up his results into a coherent and systematic scheme of knowledge and tries to guess what the whole thing means. And then next day, starting with the information he has previously obtained he sets off again in the exciting search after that ultimate completeness of knowledge that will probably never be given to man to possess. But even if this ultimate remains unattainable the results and ideas encountered during the search for it will have made that search worth while.

We have just said that the apparatus by whose aid the chemist works is "complicated-looking." We chose this rather awkward epithet advisedly for although chemical apparatus often *appears* to be complicated it is almost always quite simple in principle. Indeed one might say that the object of a piece of scientific apparatus is always to enable the scientist to investigate his materials under much simpler conditions than those that are met with in everyday life. Some of the greatest discoveries have been made with the simplest of appliances.

Lastly—a word with regard to the materials that the chemist works with. The popular idea is that they are all "chemicals"—by which is meant more or less "artificial" products of the drug store and laboratory—substances that have, so to speak, been "trained" to perform special spec-

tacular tricks. But nothing could be further from the truth. To the chemist all the materials of the whole universe furnish subjects worthy of study. Everything has properties and a behaviour that it is worth while to try to explain. Admittedly those properties and that behaviour may not in many cases be anything like so violent and vigorous as those of some of the more powerful reagents that the chemist uses: but, docile or inert as it may be, everything is from the chemist's point of view a "chemical." Starches and sugars, fats and soaps, the constituents of our foods and of our tissues are all in this sense chemicals, and many of the following pages will be devoted to a consideration of the properties of these and other such homely materials.

II

THE LIVING STUFF

It is hardly a century since microscopic studies revealed the fundamental fact that the matter of which all living organisms are composed is not in the form of one continuous mass but is made up of myriads of minute separate units of living stuff, which it has been found convenient to refer to as cells. Judged by the antiquity of some branches of human knowledge this must be regarded as a fairly recent discovery, but when one realises that these cells are so vanishingly small that a single drop of blood of the size of a pin's head contains about as many of them as New York contains of people, it will be understood that we had to wait for their discovery until the microscope was sufficiently perfected to enable us to see them.

In the bodies of complicated organisms, such as ourselves, not only is the living matter thus "organised" into cells, but the cells of one kind of tissue, when fully developed, differ very considerably in structure from those of another. For example, the cells that make up a muscle are long and cylindrical in shape, and so form tiny fibres which are characterised by their power of shortening and pulling. The pull of a muscle is just the sum-total of all the separate little pulls of its constituent fibres. Then again, nerve cells are drawn out into long filaments, or nerve fibres, which are peculiarly adapted for the transmission of the

nervous messages or impulses that pass from one part of the body to another. And lastly we might mention those cells whose function is neither contraction nor transmission, but the bringing about of chemical changes in the raw materials carried to them by the blood and the elaboration from these of products that are of some special use in the body. An organ composed of cells that carry on chemical work of this kind is termed a gland. We have but to think of the way in which the salivary glands situated round the mouth prepare and secrete the saliva which is so necessary for the digestion and the swallowing of food in order to obtain a picture of what such chemical activity means. The liver provides us with another excellent example: it is simply an enormous mass of such gland cells, and so important a part does it play in so many of the chemical changes occurring in the body that it might be referred to as the central chemical factory of the organism.

There are many other types of cell that we could go on to describe but it would be quite out of place to do so here. It is the business of the anatomist to study the forms and varieties of cells and of the physiologist to try to elucidate their various functions. The interest of the biochemist is centred in the materials of which they are composed and in the changes these materials undergo during the course of the life processes.

Now no matter what type of cell we may examine we find that it is made up to a great extent, if not entirely, of a translucent, slimy, viscous, semi-fluid material which is the living stuff itself. This is called *protoplasm,* from the Greek πρῶτος meaning "first," because it is the material of first or primary importance for the manifestation of life. Embedded in this slimy material there is to be found in every cell a roundish mass of protoplasm that is denser than the rest: this is called the nucleus of the cell. Here again we

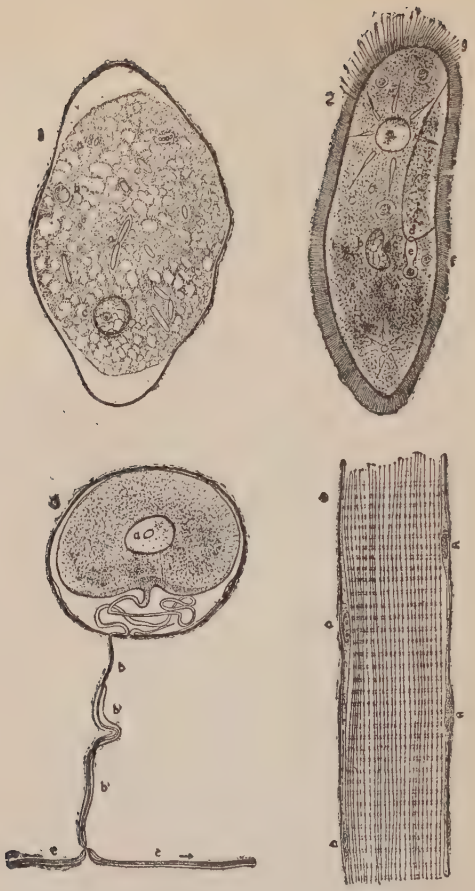

FIGURE 1. Some typical cells, very highly magnified.

1. An amœba that inhabits the human gut.
2. Paramœcium—a free-living animal whose body is made up of a single complicated cell.
3. A nerve cell.
4. A muscle fibre.

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could enter into a much more detailed treatment, and fill a whole chapter with an account of the elaborate structures of cells and of the complicated mechanisms of their nuclei; but we must refrain from so doing in order to follow our main theme of the chemical composition of living matter. However, we can take a moment to supplement this meagre account of the cell theory by a glance at figure 1 in which drawings of some typical cells as they appear under the microscope are reproduced; but for real understanding it is necessary to get in touch with some biological laboratory and see these things for oneself.

To return now to our main topic. When the chemist comes to analyse protoplasm (of course he has to use large masses of cells for the purpose, he cannot deal with them individually on account of their minute size); when he attempts to separate from one another the various constituents of which it is composed, he finds that he has before him a task that is complicated indeed. For this protoplasm is composed not of one single substance but of a mixture of many substances of very varied properties. It requires no very startling feat of chemical analysis, however, to show that by far the most abundant constituent of living matter is water. Then in this we find dissolved small quantities of mineral salts, of which the most abundant is sodium chloride—the ordinary domestic salt with which we are all acquainted. Incidentally, we might point out that the reason we eat a certain amount of this salt each day is that it is necessary to keep up the supply of this substance in the protoplasm of our tissues. In the absence of salts living matter cannot continue to function.

The next substances that the chemist will find in living matter are the fats and the sugars. If he is examining a specimen of plant protoplasm he will very likely find starches as well. Everyone knows many examples of substances belong-

ing to these groups, for we meet them every day as constituents of our ordinary food. They are the first substances we have mentioned so far that are *organic*—that is, that are typically produced by, and obtained from, living matter. Mineral salts can be obtained from the dead earth, but fat is to be got only from animals or from vegetable oils, sugar from the sugar cane or the beet-root or from fruits, and starch from such vegetable storehouses as the potato. To say that these substances are organic in nature is practically the same thing as to say that they are compounds of *carbon,* for carbon enters into the composition of all the substances that are characteristic of living organisms. It is, so to speak, the one element that has rendered life possible at all. We have but to expose any of these substances to a sufficiently intense heat in order to break up completely its chemical structure, and when we do this we at once obtain evidence that it is a compound of carbon, for this element remains as a characteristic black residue.

But even yet we have not mentioned the most essential constituents of protoplasm. When all the salts, sugars and fats have been removed there remains a mixture of substances that are much more complicated in their chemical constitution than any others we know. Being organic substances they of course contain carbon, and, as a matter of fact, oxygen and hydrogen also. But then so do the fats and the sugars. The distinguishing feature of this new group of substances is that they contain *nitrogen* as well. Now nitrogen itself is a colourless gas that is surprisingly inert and sluggish in its behaviour and does not show any marked chemical interest in anything. But once it is combined with other elements it gives rise to some very important derivatives, many of which possess remarkably vigorous chemical natures. To mention ammonia, nitric acid, such violent materials as nitro-glycerin and picric acid, and substances with

such powerful physiological actions as cyanides, quinine and strychnine, is to call attention to but a few of the intensely active substances of which this inert nitrogen is the characteristic constituent. And now we meet this apparently lifeless element as the characteristic constituent of the very substances that are essential for the exhibition of life phenomena.

These important nitrogen-containing constituents of protoplasm are called *proteins,* a name that, like the word protoplasm, is also derived from the Greek πρῶτος, for just as protoplasm is the first or essential constituent of living tissues so proteins are the first or essential constituents of protoplasm. A particular cell or mass of protoplasm may contain but little or no fat or sugar or starch, but it always contains proteins. Wherever we find life we always find proteins: in the absence of proteins life cannot be.

In order to get some idea as to what proteins are like let us think of a few examples. One of the most familiar protein materials—one that the reader is certain to know quite well already—is ordinary white of egg. This consists mainly of a strong solution of the protein called *egg albumin* (Latin *albus,* "white," hence *album ovi,* "egg white"). Everyone knows what a slimy sticky solution it is, and how widely it differs from the limpid solutions that hard crystalline substances like salt and sugar form. Everyone knows, too, its characteristic property of setting to a white solid mass—of coagulating as we say—when it is boiled. Egg albumin, then, is a *coagulable* protein: it is just one example of the large group of coagulable proteins present in all living matter. Although the fact is not quite so obvious, meat is made up very largely of similar proteins and these undergo coagulation when the meat is cooked. The proteins of blood, again, are coagulable, giving us yet another example of the widespread occurrence of these substances. But on

the other hand there are many proteins that will stand boiling without becoming coagulated. *Gelatin,* the protein that is extracted from bones and that finds such common use in the kitchen as the basis of jellies, is a well-known example of a *non*-coagulable protein. Then again *casein,* the chief protein present in milk, is another example of the same group. Everyone knows that when milk is boiled it does not set to a solid white mass. This casein can be easily separated from milk and when purified it is a white powder not very soluble in pure water but easily dissolvable in a solution of an alkaline salt such as soda. As a matter of fact in addition to casein there is in milk a coagulable protein called milk-albumin or *lactalbumin,* but there is not enough of it in cows' milk to cause any obvious amount of coagulation when the milk is boiled. In human milk, however, there is more milk-albumin than casein.

These few examples will perhaps serve to give some idea of what proteins are like, but let us emphasise again that they are but examples selected from the enormous number of proteins that are found as the essential constituents of living matter.

It is hardly necessary to point out that in order to know something about the chemical changes that occur during the life processes of an organism, we must get to know as much as we can about the chemical properties and behaviour of its proteins. That is, we must try to find out what is their chemical structure, and how they can be built up from other substances, and what products are formed when they suffer those disruptive changes that, as we have said, are going forward without ceasing in all that lives. But in the case of the proteins it is easier to state this problem than to solve it. For one thing, as we have already said, the proteins are the most complicated substances known. Then also they occur not singly but in complex mixtures. A given mass of

protoplasm will contain not merely one protein nor even proteins all of one kind; it will contain various proteins of various degrees of complexity, and although these can be roughly separated into different groups it is practically impossible in most cases for the chemist to say whether the products resulting from these attempts at separation consist of single proteins or are still mixtures of several. The proteins differ from most of the substances with which the chemist deals in being such slimy indefinite materials. Usually when a solid substance is to be purified it is dissolved up and then the resulting solution is concentrated until the substance separates out in crystals, the accompanying impurities being left behind in the liquid. But we cannot do this with proteins; they will not crystallise, so that it is practically impossible to know when we have them pure.

But lest these difficult features of the problem sound too discouraging let us hasten to add that we have been able to obtain quite a large amount of important information about the chemical constitution of the proteins even without being able to prepare them in a condition of unimpeachable purity. When the chemist is faced with the problem of elucidating the chemical constitution of a substance that is quite new to him, his usual mode of attack is to bring some of his powerful reagents—say some acid—to bear on it; to try by this means to break it down into simpler substances with which he is already acquainted and which he can easily identify. From a knowledge of the breakdown products obtained in this way he can form a fairly complete idea of the chemical structure of his original new substance; and very often he tries to confirm this idea by attempting to put the fragments together again and to reconstruct the original complex. This mode of investigation has been applied with success to the study of the chemical constitution of the proteins. If we take a solution containing a protein—

white of egg, casein, gelatin or any of those we mentioned will do—add to it a little acid and then stew up the mixture for several hours, we find that the originally viscous slimy mixture slowly becomes more and more limpid; the protein of the egg white is being broken down into simpler products under the action of the acid until at last none of it remains unchanged. It is from the products now present in the solution that we can obtain our much desired information with regard to the chemical structure of the original egg protein.

What then, are the products that we do actually obtain? To an audience of chemists the answer could be expressed in one word—*amino-acids;* but to those interested laymen who may here be meeting this technical term for the first time a full explanation of its meaning is due. It unfortunately denotes so much that it must be explained at some length, but if the reader will bear with me for a paragraph or two I will try to give him an account of what is certainly one of the most fundamental discoveries that biochemists have to their credit.

Let us start from facts that are well known to everybody. Everyone knows that ordinary domestic vinegar contains considerable quantities of an acid, and many know that this acid present in vinegar is named *acetic acid,* after *acetum,* the word which the old Latin housekeepers used when they went to purchase this tasty condiment in the department stores of ancient Rome or their branch establishments in Pompeii. This acetic acid when pure is a colourless liquid resembling water in appearance but possessing a strong, pungent, vinegary odour. Now acetic acid is but one member of a long series of similar acids that all exhibit the same general chemical properties. Another of them occurs in butter and is liberated in the free condition when the butter becomes rancid. This one is called

butyric acid, from another household word among the Romans, namely *butyrum,* their name for butter. Anyone who knows the smell of rancid butter will be familiar with the odour of butyric acid. Yet another acid belonging to the same series is the *stearic acid* which occurs in many animal fats, particularly in suet. Stearic acid is the material from which "stearine" candles are made. It differs from acetic and butyric acids in being not a liquid but a white greasy solid. Now these three acids are but examples of a long series of acids, the simpler members of which are limpid liquids resembling water, the intermediate members viscous liquids more like oils, and the final more complicated members white fat-like solids. As many of these acids occur in fats the whole series is usually referred to collectively as the *fatty acids.* They are, of course, all organic acids: they are all compounds of carbon produced by or occurring in living organisms. Strong acids they certainly are not in comparison with the powerful corrosive inorganic acids like sulphuric, nitric and hydrochloric; but they all possess the typical acid property of combining with bases such as soda to form salts. Ordinary soap in fact is nothing more than the compound of stearic acid with soda, though it is often much disguised with colour and scent.

We have described these fatty acids somewhat fully because they are the parent substances of the amino-acids. An amino-acid can be described as one of these fatty acids in which we find nitrogen incorporated as part of its chemical structure. Naturally the presence of this nitrogen modifies very considerably the properties and behaviour of the original acid. Its acid properties, for example, feeble before, are now even weaker still as a result of the presence of the new element. But what is perhaps of most significance from our immediate point of view is that these amino-acids are white solid substances that crystallise quite readily from their so-

lutions, so that they can be easily separated, purified and identified.

Now it so happens that when we take the mixture obtained by decomposing a protein by stewing it up with acid in the way already mentioned, and submit it to these processes of crystallisation and separation and purification, we find that it contains some dozen or more of amino-acids. Some of these are not so simple in composition as the reader may have gathered from what was just said about the combination of nitrogen into the chemical structure of fatty acids; many of them contain other and more complicated groups in addition to the nitrogen; others contain other elements—such as, for example, sulphur. But no matter what other complications of structure may be present in particular cases, they all agree in consisting essentially of fatty acids into the chemical structure of which nitrogen is built as a characteristic constituent. Moreover, the nitrogen that we found to be so important and characteristic a constituent of a protein is really the nitrogen of all the amino-acids of which the protein is composed.

The next point to notice is that it matters little what particular protein we break up in this way, we always obtain a mixture of roughly the same dozen or so of amino-acids. Whether we start with egg white or with the proteins of, say, blood, or muscle, or milk we obtain a very similar mixture in the end. Certainly, the proportions in which we should obtain the various amino-acids would be somewhat different according to the protein selected for the experiment; for one protein may contain an abundance of a certain amino-acid while another protein may contain little or none of it but more of a second, and so on. But in general we can say that no matter what protein we decompose we shall always get some at least of each of the same dozen amino-acids as any other protein would yield.

The question now immediately presents itself: What is the relation of this mixture of amino-acids to the complicated intact chemical structure of a protein? The most obvious answer is the one that is now regarded as the true one: namely that, since proteins when thus more or less gently decomposed yield these amino-acids, then these amino-acids must represent unchanged fragments of the original protein structure. In other words the amino-acids are not formed by any far-reaching rearrangement of the ultimate constituents of the protein during the decomposition, but exist, linked together by chemical forces, in the complex structure with which we set out; they are the units out of which that structure is built. A protein is simply an enormous complex of amino-acids all united chemically to form a complicated whole. We may say that a protein is built up of a variety of amino-acids just as a building is made up of a variety of kinds of bricks and stones; and just as a heap of disconnected bricks and stones differs from a building, so does a mere mixture of amino-acids differ from a protein: in each case the individual units must be united before the final structure appears. But that we know all there is to know about the way in which these amino-acid units are united and arranged in the protein edifice, those who are most familiar with this subject would be the first to deny.

We said a little while ago that when the chemist has broken down a substance into its constituent units in order to make sure that his guess as to the exact arrrangement of these units in the structure of the parent substance is correct, he tries to cause them to recombine according to his ideas and so attempts to regenerate the original material. If he succeeds in bringing about this process of building up or *synthesis,* and does actually obtain the substance from which he started, then there can remain little doubt as to the truth of the ideas he at first derived from his study of the prod-

ucts obtained by his original process of breaking down or *analysis*. Not unnaturally the chemist has been curious to see whether in the case of proteins he could achieve any success with such a process of synthesis, and could cause amino-acids to re-combine to give him anything like a protein again. As a matter of fact, a certain amount of success has already followed such an attempt. Amino-acids have been caused to combine one by one until a complex consisting of as many as eighteen units has been obtained, and it was found that as more and more amino-acids were linked together in this way the product began to show more and more resemblance to some of the simpler proteins. But even so this substance was probably very much simpler than even the simplest proteins that occur in nature, for in the eighteen proportions of amino-acids that went to its make-up only two varieties of amino-acids were represented. One of these was used fifteen times and the other only three. As we have seen, the naturally occurring proteins are built up of a much greater variety of kinds of amino-acids than this.

It is evident that in this process of synthesis the chemist is confronted with difficulties far greater than those he is accustomed to meet with elsewhere. For while he has a dozen or so of amino-acids to deal with, our present knowledge gives him but little guidance as to the order or arrangement in which he should try to induce them to combine. The properties of the substances produced by their combination will of course differ very considerably according to the particular pattern of the arrangement, just as the character of a building will depend on the the actual arrangement of its constituent bricks and stones. And when we remember that the chemist is not confined to the use of only one proportion of any of the amino-acids, but finds the same amino-acids in widely differing proportions in the various proteins, we shall realise that the number of possible combinations that

could be made from even this dozen of comparatively simple substances amounts to many bewildering millions.

Herein lies the clue to the existence of that almost infinite variety of proteins which we find in the myriad species of living creatures that share our planet with us. There is much we shall need to know about proteins and about the way in which their constituent amino-acids are combined, before we can ever hope actually to build up any one of them completely in the laboratory. Nevertheless the information we already have, the recognition of the amino-acids as the units of protein structure, has given us something of that far-reaching insight into the behaviour of proteins which is fundamental to the understanding of the behaviour of cells, and so of the behaviour of tissues, and so again of the behaviour of organisms themselves.

III

SUGAR, STARCH AND FAT

Now that we have said enough about the proteins to serve for the time being, we must retrace our steps a little and devote just a short chapter to a consideration of some of the more important facts about those substances of biochemical interest that are devoid of nitrogen. From what we have already said the reader will remember that these include the sugars, starches and fats. Fortunately, as these materials are in everyday use, our task will consist merely in adding a few more details to what is generally known by everybody.

The sugar with which we are all most familiar is, of course, *cane sugar*. It is present ready-formed, not only in the juice of the sugar cane but also in that of the sugar beet. From these sources it has merely to be extracted and purified. It is also found in the sap of the maple (maple syrup and maple sugar) and in many fruits. We know it as a very well defined substance that dissolves readily in water and can be easily crystallised and so purified. The great thing to be realised about this substance is that it is but one member of an enormous group of substances all more or less similar in their general characteristics. And of this group of sugars cane sugar is by no means the simplest member. If we adopt the same method of investigation as we employed in the case of the proteins and heat a solution of

cane sugar with a little acid—in this instance a few minutes will suffice—we find that the cane sugar is quickly resolved into two simpler sugars. One of these is *glucose,* a substance of such great physiological importance in living matter that we shall have a great deal to say about it before we arrive at the end of this volume: among other things it is the sugar that is always present in the circulating blood. When pure, glucose is a white crystalline substance, but for trade purposes it is often not necessary to purify it so thoroughly, so that it is often obtained in the form of a brownish cheesy mass or as a thick syrup. Its taste although distinctly sweet is not at all so sweet as that of cane sugar. The other sugar that is formed when cane sugar is split into its constituent simpler sugars is called *fructose,* or fruit sugar, but as it is not very important so far as the body is concerned we shall content ourselves with just this mention of it. What we have said so far may be summarized in the form of an equation thus:

$$\text{cane sugar} \longrightarrow \text{glucose} + \text{fructose}$$

Let us then go on to notice the sugar that occurs in milk. Again we have to thank the old Roman housekeepers for providing us with a name, for this milk sugar is called in scientific language *lactose,* from the Latin *lac, lactis,* "milk." Milk sugar, again, is not one of the simplest of sugars but, like cane sugar, it belongs to the group of sugars that can by fairly simple means be broken down into two. In this case, as in that of cane sugar, one of the constituent sugars is glucose; but the other is a sugar named *galactose*—in this case it is the Greek word for milk (γαλα, γαλακτος) that furnishes us with a name—about which there is little we need say apart from noting that it occurs in some of the complexes that are constituents of nerve fibres:

$$\text{lactose} \longrightarrow \text{glucose} + \text{galactose}$$

Now we come to the starches. Starch, as is well known, is a substance that is manufactured by plants, and stored as a reserve of food material in various parts of their bodies. As in so many other cases, man here takes advantage of the industry of other organisms and breaks in upon their treasured stores and uses them for his own benefit. Thus it comes about that those parts of plants that are richest in starch are in many instances very valuable foodstuffs. Wheat has become the staff of life because the wheat plant during its life stores its seed, the wheat grain, so richly in order to provide for the nourishment of the embryo wheat plant of the next generation during the first stages of its growth. Seeds and fruits are by no means the only parts of plants in which starch is stored as a reserve material. In the sago palm the storage takes place in the pith of the stem; while in the potato special underground tubers are developed that serve to house the supply. In all these situations the starch occurs not as crystals but in grains of a peculiar roundish shape which bear rings indicating the way in which they have been built up layer on layer in the plant cell. These grains are not affected by cold water because their outer layers are insoluble, but when hot water is poured on to them they swell up until their outer coats burst and then the soluble starch from inside dissolves up, forming the starch paste that is used so extensively in the laundry. The same bursting of the grains occurs also when starch is cooked, and this is important because it renders the starch much easier to digest.

From the fact that starch cannot be caused to crystallise one would guess that it must be a complicated substance, and this surmise is, as a matter of fact, correct. Complexity of chemical structure and difficulty of crystallisation often go hand in hand. When starch is broken down, as it can be by heat or the action of acids, a long series of products is

obtained. The starch gives rise first to somewhat simpler substances called *dextrins*. The reader will now be able to understand what is meant when the manufacturers of cereal foods state that their products are "dextrinised." It means that in them by suitable heating the starch has been partly converted into dextrins. Now dextrins are much easier to dissolve than starch, so that this process of dextrinisation is obviously of advantage from the point of view of the digestion of the food. Dextrins, also formed by the action of heat on starch, are present in the crust of a loaf of bread and in toast. They are also formed during the process of ironing starched linen, the heat of the iron converting the starch into dextrin which imparts the desired gloss and finish to the shirt front. As dextrins are sticky substances they find a use in the manufacture of adhesives.

Now when the dextrins themselves are broken down we obtain a sugar called *maltose* or malt sugar: this is a typical sugar with a sweet taste. It is present in malt because when the barley grain germinates the starch it contains is decomposed along the lines we have been describing. When this malt sugar is in turn broken down we obtain from it nothing but glucose, so that we conclude that maltose is itself a compound of glucose with glucose just as cane sugar is a compound of glucose and fructose. The dextrins, then, are more complex chemical aggregates in which the unit of structure is still glucose, while starch itself is a yet more complex substance built up also from nothing but glucose. Expressing all this in an equation we have:

$$\text{starch} \longrightarrow \text{dextrins} \longrightarrow \text{maltose} \longrightarrow \text{glucose} + \text{glucose}$$

We might mention that this breaking down of starch by means of acid is the method used for obtaining glucose in large quantities for trade purposes. From what we have said it will now be evident why this commercial glucose is

often obtained as a brownish cheesy mass; it is because the decomposition of the starch is usually not quite complete so that a certain amount of dextrin remains in the final product. For many of the purposes for which glucose is used the presence of this dextrin is of little consequence and therefore no great trouble is taken to remove it.

The starch that we find in plants is not the only starch with which we are acquainted. In the liver and also in the muscles of animals we find abundant quantities of what is called *animal starch*. This is known to be a different chemical substance from the starch of plants, for it has somewhat different chemical properties. Nevertheless it also consists of a complex made up entirely of glucose, for in the body and also in the laboratory it can be easily broken down to give nothing but this sugar. This fact is intended to be expressed in its scientific name, *glycogen*, "the sugar producer."

Just one more point before we leave our study of these starches and sugars for the time being. If we take any one of the substances about which we have spoken so far in this chapter and break it down completely—say by heating it strongly—we find that it is ultimately composed of carbon, hydrogen and oxygen, and no matter whether we do this with starch or glucose or milk sugar or any of the others we find further that the hydrogen and oxygen are always present in the same ratio as that in which they unite to form water. Everybody knows that water is a compound of hydrogen and oxygen, and that in water there are two atoms or units of hydrogen to one of oxygen, expressed by the formula H_2O. Now it is just in this same proportion that we always find the hydrogen and oxygen to be present in a starch or sugar—two atoms of hydrogen to one of oxygen. For this reason one could regard these substances in a crude kind of way as compounds of carbon and water, and so it

has come about that the whole group has received the name of *carbohydrates*. We know very well nowadays that the starches and sugars are not really merely compounds of carbon and water as this name would suggest, but the word is in such general use that it is convenient to continue to use it although it really expresses an old and erroneous idea. So far, then, in this chapter we have been studying the properties of a few members of the large group of carbohydrates. Before we leave them there is just one more of them that we must consider, although it is, strictly speaking, neither a sugar nor a starch.

In Chapter II we explained that the body of an animal or plant is made up of myriads of tiny units of living matter known as cells. Now in animals these cells are usually naked; each lies next its neighbour with no very obvious partition between. But in plants the cells almost always have walls; that is, each cell is enclosed in a little box or compartment, so that the whole tissue is very much like a honeycomb on an extremely small scale. It is not surprising that this network of *cell walls* should have been discovered very early, even at a time when microscopes were very imperfect. Indeed the name cell was given to the compartments long before the importance of their contained protoplasm was realised. What interests us here is that these walls of plant cells are composed of a carbohydrate known as *cellulose,* which has been shown to be, like starch, a complex substance built up entirely of glucose units. The reader may not have actually seen cell walls in plant tissues, but he has often seen the material cellulose itself. In fact he is looking at it now, for it is the material from which paper is made. Paper is simply cellulose obtained from wood by pulping and milling into sheets. Cotton is also practically pure cellulose. Not only cellulose itself but also its chemical derivatives are important technical products. When it is acted upon

by strong nitric acid, *nitro-cellulose* or gun cotton is formed, and this has the useful property of burning very rapidly, i. e. exploding, when ignited even in a confined space shut off from the air. These nitro-celluloses are also used as the basis of celluloid (hence the inflammability of this material and the danger of fire from movie films) and by various processes they can be spun into fibres forming artificial silk as well.

We must now pass on to say something about the fats. The fats with which we are most familiar are those that are constituents of our everyday foods. Some of them, as, for example, mutton fat (suet) are fairly firm white solids at ordinary temperatures; others, such as pigs' fat (lard) and the fat of milk (butter) are soft and semi-fluid; while the fats of vegetable origin such as olive oil are usually liquids. They are proverbially insoluble in or immiscible with water. If one wants to dissolve a fat one has to use an organic solvent such as ether or chloroform. Hence the use of such solvents for removing grease spots from clothes. But although they will not dissolve in water they can be distributed through water in the form of minute floating droplets, thus forming what is known as an emulsion. It is in this form that the fat is present in milk.

To say that when fats are analysed we find that they consist of carbon, hydrogen and oxygen, and that they contain a relatively much smaller proportion of oxygen than the carbohydrates do, is to give a very imperfect statement of their chemical relationships. We obtain much more valuable and significant information if we break them down much less drastically into their components rather than into their ultimate constituents. This gentler decomposition could be brought about by heating with a little dilute acid as in the case of the other substances we have already studied in this way, but in the case of the fats it is more effective to

use an alkali such as caustic soda (lye) for the purpose. If some fat is boiled with a solution of caustic soda for a time it gradually dissolves in the alkaline liquid, and we obtain a mixture in which we can search for the products into which the fat has been decomposed. When we analyse the mixture obtained in this way we find that one of its most characteristic constituents is soap. Indeed the ordinary method for manufacturing soap is by boiling fat with caustic soda. Now we mentioned briefly on page 31 that ordinary soap is the "salt" formed by the combination of soda with *stearic acid*, and that stearic acid is one member of the series of fatty acids. When therefore we find soap as an important product of the destructive action of caustic soda on a fat, we conclude that what has happened is that stearic acid has been liberated by the disruption of the chemical complex of the fat, and that this acid has then at once combined with the soda to form the soap. As a matter of fact, there are a few others of the fatty acids related chemically to stearic acid and resembling it in general properties that are also found in fats. Of such acids we might mention *palmitic acid*—a very near relative of stearic acid—and also *oleic acid* which is from some points of view a more distant relation. These also combine with soda to give their corresponding soaps, and in the decomposition mixture of a fat we usually find the soaps of all of these three acids at the least. In some fats we find other acids as well—in butter, for instance, butyric acid; but the three acids we have mentioned—stearic, palmitic and oleic—are the ones that occur most commonly in the ordinary fats. One kind of fat differs from another mainly in the proportions in which these acids are contained in it and may be obtained from it, but most kinds of fat contain some of all three. The case is somewhat similar to that of the amino-acids and the proteins, but is much simpler really as we have far fewer

constituents to deal with. It is usually found that the more solid fats such as suet yield the greatest proportion of stearic acid (Greek στερεος, "solid") while oleic acid is found in greatest amount in the more liquid fats such as lard and olive oil—indeed it is from its occurrence in vegetable oils that oleic acid obtains its name (Latin *oleum,* "oil").

But we have yet to mention the other important constituent that is set free when a fat is decomposed by soda. It is glycerin—or, as it is more scientifically called, *glycerol.* This remains behind when the soaps have been removed by appropriate means from the reaction mixture. There is little need to describe its properties: everybody knows the heavy, syrupy sweet-tasting liquid. All fats yield glycerin in addition to fatty acids when their chemical structure is disrupted, so that we come to realise that a fat is a compound of several fatty acids with glycerin. When the fat is boiled with soda the fatty acids and the glycerin are forced to part company and the fatty acids are at once converted into soaps in the way we have already described. We can summarise the whole process in a few words:

fat $\longrightarrow$ fatty acids + glycerin
fatty acids + soda $\longrightarrow$ soaps.

Of course these equations summarise not only what takes place on a small scale when the chemist examines a fat in the laboratory, but also what occurs on a scale involving thousands of tons of material in the manufacture of soap. This amount of information with regard to the chemical structure of fats will be sufficient for our present purposes, and as we have now made a brief study of the chemistry of the chief kinds of materials that enter into the composition of living matter we are now in a position to consider the parts that they all play in the varied manifestations of life phenomena.

IV

FOOD

To a casual observer it might seem that humanity as a whole is tending more and more to obey the scriptural injunction forbidding undue anxiety regarding such material necessities of life as food and drink. Many of us accept unquestioningly food prepared for us by others without a thought as to its suitability or its significance. We leave instinct to decide the amount of nourishment that we shall take each day, and, on the whole, perhaps, we do not err grossly or for long at a time. For even when the modern emancipated business girl attempts to live on nothing but ice cream, cocktails and candy, instinct soon comes to the rescue and creates a craving for a more adequate and satisfying menu.

But man has not always been able to take so superficial an interest in his food. In his wilder primitive state the hunting and capture of food were activities which, together with personal defence, occupied most of his waking moments. And even now this indifference to food is by no means universal, for, obscure the truth as we will, there are sections of the human race whose energies are entirely absorbed in a struggle for mere bread, a struggle, moreover, that is devoid of the exhilaration and romance of the chase and is often unparalleled in its sordidness and despair.

The scientist, also, has not been indifferent to the sub-

ject of diet, with the result that, whatever may be the case in other branches of human intellectual activity, in this field at least we can claim to have made advances which, even if they have not been applied sufficiently extensively to increase the sum total of human happiness, have certainly helped to diminish the suffering caused by our backwardness in other spheres. In beginning our account of the modern teaching on the question of diet we will point out to the reader something that he has already partly realised for himself—namely, that when in previous chapters we were describing proteins, sugars, starches and fats we were at the same time giving an account of the chief constituents into which the diet of even the most fastidious gourmet can be resolved. The constituents of our food are substances similar in their chemical relationships to the constituents of our bodies. Not that this realisation should occasion any surprise, for we might have expected that the body would require for its maintenance substances similar to those of which it is composed. But what exactly do we mean by maintenance when we are referring to the body? What is the nature of the process that this term is used to denote? It is evident that we must possess the answer to this question before we can proceed far with our study of food and its uses.

Without disparaging the work of earlier investigators it must, I think, be admitted that we owe the beginnings of our present-day knowledge of the general chemical processes that are continuously going forward in the animal body to the researches of the French scientist, Lavoisier, who worked during the last decades of the eighteenth century. His outstanding investigations were concerned with the composition of the atmosphere and the chemical changes taking place during the burning of a fire. It was he, as perhaps many of my readers will know, who first showed that a sub-

stance when it is burning is combining with oxygen—the active constituent of the air—and that the heat given out during the combustion is evidence of the vigour of the intensity of their mutual affinities. But in Lavoisier's time the study of nature was not divided into separate sciences and departments all housed in separate laboratories. Each individual worker usually included a very wide range of topics within the scope of his investigations and so acquired a broadness of outlook that is difficult to obtain amid the specialisation of to-day. Lavoisier's experiments were by no means confined to non-living materials. He showed that in the living body a similar process of combustion is continuously proceeding, and realised that the warmth of the body is a product of this living fire. From this conclusion it was an easy step to the realisation that the fuel that goes to feed this fire is obtained from the food that the individual himself eats. As Lavoisier himself says: "The animals which respire are truly combustible bodies which burn and consume themselves." "Since in respiration it is the substance of the animal itself, it is the blood, which furnishes the combustible, if the animals do not repair by their aliment that lost by respiration the oil would be lacking just as in a lamp; the animal would perish like a lamp extinguished when it lacks nourishment." Not only the scientific truth but also the poetry of this conclusion has caught the imagination of thinkers and writers, and they have expressed it in varied ways according to the type of their art. Let us quote Oliver Wendell Holmes' delightful old professor before we pass on. Says he: "The human body is a furnace which keeps in blast three-score years and ten, more or less. It burns about three hundred pounds of carbon a year (besides other fuel), when in fair working order, according to a great chemist's estimate. When the fire slackens, life declines; when it goes out, we are dead."

The reader who has followed our description of the chemistry of sugars, fats and proteins will remember that all of these substances contain an abundance of carbon and hydrogen, and it is these constituents that constitute the fuel of the body. When carbon burns in air it unites chemically with the oxygen to form *carbonic acid gas* or *carbon dioxide*—a process which, not using any chemical formulas, we shall express briefly in another of our word equations thus:

carbon + oxygen ⟶ carbon dioxide.

When this combustion of carbon takes place in an ordinary fire, the amount of heat energy liberated is sufficient to make the burning mass red- or even white-hot. In the body the oxidation of carbonaceous substances proceeds through many intermediate stages and the energy is liberated much more gently, but nevertheless the end results are the same. There can hardly be any of my readers who has not at some time carried out the well-known experiment of bubbling his expired breath through clear lime water by means of a tube held in his mouth and thereby observed the liquid turn milky as the lime is converted into calcium carbonate (chalk) by uniting with the carbon dioxide he is producing.

Similarly, hydrogen burns in air with such energy that a violent explosion takes place when a mixture of the two is fired. The end product in this case is water, which usually escapes in the form of vapour:

hydrogen + oxygen ⟶ water.

Everybody knows that when a flame is brought to bear on the cold surface of a kettle or saucepan water is condensed on to it just as water can be similarly condensed from the expired breath. In each instance the water has been produced by the combustion of the hydrogen of the fuel materi-

als, albeit the process is again more gradual in the body than is usually the case in the chemical experiment.

One of the foremost uses of food to the body is thus to serve as fuel for the combustion that is throughout life taking place in its every part.

But body warmth is not the only form of energy that is obtained by the combustion of food. Lavoisier showed that when a man carries out work by means of his muscles the rate of combustion in his body is increased. This means that the muscles obtain the mechanical energy they use for all the varied movements of daily activities from the energy that is set free during the burning up of materials within themselves, and we shall see later the exact correspondence between the amount of work the body does and the amount of combustion that takes place in it during that work. The body is therefore a kind of internal combustion engine whose fuel is obtained from the food it takes in.

But yet again, the production of warmth and mechanical energy by combustion is not the only use of food. It is evident, for example, that in a growing child it is from the food that the body obtains the material for its steady increase in size, i. e. for the formation of new living matter. Even in a fully grown adult the living matter is not fixed and stable: as we have mentioned in previous chapters, it is subject to a continuous process of disintegration, so that unless the food contains such materials as are required to make good the loss the body must steadily decline in weight and waste.

Now the question of questions that confronts us in this chapter is: How much shall we eat and of what? and it will now be evident that in order to be able to give advice as to how much of beef, potatoes, bread and butter a man should eat per day we must first know what are the constituents that go to make up an ordinary diet, how much energy can be obtained by the combustion of known amounts of these

constituents, and to what extent they are suitable for making good the wear and tear of active living tissues. This sounds like a comprehensive programme, but it is only when we possess all this information that we can give a satisfactory, reliable answer to the problem we have propounded for ourselves.

Of course we could obtain a certain amount of information by referring to an obviously well-nourished and active individual and studying the nature and amount of the food he consumes, and this information would certainly be of value. Tradition—the accumulated experience of the race—and instinct—the unreasoned but appropriate behaviour of the individual—might well bring us near the truth on such a matter. But this method of approach has its limitations: it gives no far-reaching insight into the fundamental processes involved, and when it comes to saying what is wrong with the diet of an obviously ill-nourished person it fails completely. In order to give a scientific answer, i. e. an answer based on all the well-proven knowledge we can obtain, we must find out the needs of the body under various conditions for both materials and energy; we must know how much of these needed materials our ordinary articles of diet contain, and how much energy they are capable of yielding when submitted to the process of combustion in the body. Only then shall we be in a position to elucidate and apply the scientific principles underlying the processes we are observing.

To begin with the question of the composition of foods. We have already pointed out that the constituents of our ordinary foods belong to the same classes of chemical substances as do the constituents of living tissues, and indeed a moment's reflection will show that many of our articles of food are actually composed of the tissues of other organisms on whose reserves we prey in order to satisfy our own needs. Consider, for example, a joint of beef: this consists

mainly of the muscular tissue of the ox, and, from what we have already said about the importance of proteins in the make-up of living tissues, the reader will not be surprised to hear that beef, and, with it, mutton, pork and the other meats we eat, contains a very considerable proportion of proteins amounting to something like 20 per cent of the total weight. The meat foods thus come to constitute the chief sources of protein to the body. Every kind of fish also, of course, contains a high percentage of protein, and the same is true of eggs. Some vegetable foods also contain a fairly high proportion of proteins—particularly such articles as peas and beans. In these seeds the parent plant has stored up proteins, among other foods, for the nourishment of the future embryo plant which, did we not intervene, would ordinarily use them during its development. But all except vegetarians rely on plant foods mainly as sources of starch and sugars rather than of proteins. For example, in the wheat grain some protein is stored but by far the most abundant reserve food material for the embryo is in this case starch. Thus it comes about that more than half of a loaf of white bread is starch. Then again, a potato is a swollen underground portion of the stem of the plant loaded up with starch to the extent of 16 per cent or more of its weight. It is hardly necessary to say that fruits as a rule contain sugars, which in most cases serve to attract birds and other animals who distribute the pips or seeds of the fruit, passing them unchanged through their alimentary canals. When we transport a Canadian apple some thousands of miles it is because we desire the delectable sugary pulp which the plant has, so to speak, provided as a bait in order to secure the contained seeds a safe transit over a journey that they would of themselves be quite incapable of making. But of course the thing is somewhat overdone in these days for we usually import apples to the places where they will not grow, so

that the seeds have but scant chance of survival when the adventurous journey is done.

Green vegetable foods—such things as cabbages and salads, for example—contain but little of any stored foodstuff, but are important sources of the vitamins to which we shall devote considerable space later (Chapter XIII).

We have yet to mention the sources of fat. We get most of this from our animal food—with our meat and bacon and in the form of butter and cream. Fish foods vary greatly in the proportions of fat they contain. In the flesh of the "lean" fishes such as cod, haddock and whiting there is less than 1 per cent of fat, and in the flat fish, such as plaice or flounder, the percentage amounts barely to 2. In contrast with these we have the "fat" fishes, herring, mackerel, salmon and sardines, whose flesh contains at least 10 per cent of fat. This is how it comes about that from the point of view of supplying fuel to the body the herring is so much better value for money than the cod which stores all his fat in a part of him that we do not eat, namely the liver. Some of us get a certain amount—and the Italians get quite a large amount—of vegetable fat from the oil stored in olives but this is for many folk something of an acquired taste.

We ought also to say a word about the milk which forms our first diet. It contains not only the numerous globules of fat that give it its characteristic opaque white colour but dissolved proteins, milk sugar (see p. 37) and lime salts as well. It thus contains all the chief essentials of a complete diet, and indeed furnishes all the materials from which the growing infant builds up all its new tissues. But for adults it contains an inconveniently large proportion of water. We therefore ferment it in various ways and obtain from it a more concentrated food—cheese—which contains most of the protein and all of the fat of the original milk and so is

not only a traditional but also a scientifically justified addition to the starchy bread which it usually accompanies.

Human milk contains constituents similar to those of cows' milk but in rather different proportions. In both there is the same proportion of fat; in the human product, however, there is much less protein but more milk sugar. In order, therefore, to make cows' milk more suitable for feeding infants it has to be diluted with water in order to bring the protein percentage down to the correct figure, and then extra sugar and cream must be added to bring up the concentration of these constituents again. But even a milk "humanised" in this way is not an exact imitation of human milk, for, although its total percentage of proteins may be right, the relative amounts of the individual proteins will not be so. On page 28 we mentioned that in milk there are two chief proteins—casein and milk-albumin. In cows' milk there is much more casein than albumin, but in human milk the albumin is in excess. It is better, therefore, to dilute the cows' milk not with water but with whey, which is the liquid left over after cheese has been made from the milk. This contains only milk-albumin and milk sugar, all the fat and casein having been removed in the cheese. By the use of whey a mixture may be made in which the proportions of the proteins are the same as in human milk, and from which, by the addition to this of some cream and a little more sugar, a satisfactory substitute for the natural product may be obtained.

By these few examples we have tried to show how foods can be analysed into varying proportions of protein, carbohydrate and fat. At the present time most of the materials that are used as human food have been examined in this way so that we know how much of each of these fundamental constituents is contained in anything we are likely to want to eat. In order to give the reader enough of this enor-

COMPOSITION OF TYPICAL FOODS

This table gives the percentage of Proteins, Fats and Carbohydrates in the *edible portion* of each food-stuff: the residue, consisting of water, mineral salts and indigestible material, is not recorded.

Food	*Protein* %	*Fat* %	*Carbohydrate* %
MEATS			
Bacon, smoked	10.5	64.8	–
Beef, brisket	15.8	28.5	–
steak, lean rump	20.9	13.7	–
liver	20.4	4.5	1.7
suet	4.7	81.8	–
Chicken, broilers	21.5	2.5	–
Ham, smoked	16.5	38.8	–
Lamb, leg	18.6	22.6	–
Pork, loin chops	16.4	32.0	–
Sausage, Frankfort	19.6	18.6	1.1
FISH AND SHELLFISH			
Cod, whole, average	16.5	.4	–
Halibut, steaks	18.6	5.2	–
Mackerel	18.7	7.1	–
Salmon, whole average	22.0	12.8	–
Sardines, canned	23.0	19.7	–
Lobster, canned	18.1	1.1	.5
Oyster, in shell	6.2	1.2	3.7
DAIRY PRODUCTS			
Butter	1.0	85.0	–
Cheese, Cheddar	27.7	36.8	4.1
cream	25.9	33.7	2.4
Cream	2.5	18.5	4.5
Eggs, uncooked	13.4	10.5	–
Milk, whole	3.3	4.0	5.0
Oleomargarine	1.2	83.0	–

Food	*Protein* %	*Fat* %	*Carbohydrate* %
VEGETABLES			
Beans, dried	22.5	1.8	59.6
lima, dried	18.1	1.5	65.9
string, fresh	2.3	.3	7.4
Beets, fresh	1.6	.1	9.7
Cabbage	1.6	.3	5.6
Carrots, fresh	1.1	.4	9.3
Corn, green	3.1	1.1	19.7
Lettuce	1.2	.3	2.9
Onions	1.6	.3	9.9
Parsnips	1.6	.5	13.5
Peas, green	7.0	.5	16.9
Potatoes, white, raw	2.2	.1	18.4
sweet, raw	1.8	.7	27.4
Squash	1.4	.5	9.0
Turnips	1.3	.2	8.1
FRUITS			
Apples	.4	.5	14.2
Bananas	1.3	.6	22.0
Oranges	.8	.2	11.6
Pineapple, canned	.4	.7	36.4
Peanuts	25.8	38.6	24.4
CEREALS			
Bread, wheat, white, average	9.2	1.3	53.1
Crackers, average	10.7	8.8	71.9
Flour, wheat, average high and medium grades	11.4	1.0	75.1
Oatmeal	16.1	7.2	67.5
Rice	8.0	.3	79.0
Shredded wheat	10.5	1.4	77.9
Macaroni	13.4	.9	74.1
SUGARS, ETC.			
Marmalade, orange	.6	.1	84.5
Molasses, cane	2.4	–	69.3
Syrup, maple		–	71.4
Sugar, granulated	–	–	100.0

mous mass of information to enable him to take an intelligent interest in his food without giving him mental indigestion we have collected together in the table on pages 54 and 55 particulars of the composition of the commoner foods. In using this table it must be borne in mind that the values apply not to the crude food as it is bought, but *to the part of it that we actually eat.* From the point of view of economy in expenditure on food it is of course very necessary to know how much waste there is in each pound of food we buy—how much of a joint of meat is bone, how much of an egg is shell, how much of a pint of milk is water, and so on. But for the study of the biochemical principles of nutrition it is what a man eats that counts and not what he spends on it. Then also it must be realised that the composition of any food-stuff is by no means the same from sample to sample: the proportion of fat in meat, to take one example, varies enormously according to the condition of the animal and the particular cut taken. We have, therefore, tried to give a fair average value for each article.

If the reader is interested in some article of diet that is not listed he should turn to the source from which we have obtained our information, namely: *"The chemical Composition of American Food Materials"* by Atwater and Bryant. This is Bulletin No. 28 (revised 1906) of the U. S. Department of Agriculture and can be obtained for 10 cents and postage from the Government Printing Department, Washington, D. C.

For English foods there is a similar compilation by Plimmer, entitled: *"Analysis and Energy Values of Foods."* This is a British Government publication and can be obtained from H. M. Stationery Office, Imperial House, Kingsway, London, England, for 6 shillings.

But merely to look at a table like this is not half so interesting or instructive as to make practical use of the in-

formation it contains, and in order to do this the reader need only provide himself with a fairly sensitive balance which he can have on his dining table and by means of which he can, whenever he gets a day sufficiently quiet for the purpose, weigh the amount of each food-stuff he eats. The most suitable instrument is a letter balance capable of weighing at least to 1 lb. and giving the weight directly by means of a pointer on a scale (i. e. without "weights"); the least troublesome way of using it is to have the various foods on separate saucers or small plates and to weigh each saucer with its contents before the meal and then again when the desired amount has been eaten. The pairs of weighings are to be jotted down so that the actual amount of each food taken can be at once obtained by performing the subtractions. In this way one can determine the exact amount of potatoes, meat, bread, butter and so on, that one eats during the course of a day. The next thing is to look up in the table the percentage of protein, fat and carbohydrate in these various foods and, with the aid of these numbers and a little skill in multiplication, to calculate the total amounts of each of these constituents used. It is really more scientific to weigh and calculate these quantities in grams, as the metric system of weights and measures is used for all scientific purposes, but it will do just as well if they are in ounces and decimal fractions of an ounce. If the reader will carry this through he will have performed his first experiment in the science of dietetics, and will have obtained a result that will have far greater interest for him than any imaginary example that we might choose for purposes of illustration, for it is a result that applies to himself personally and that he has obtained from his own observations. Of course some difficult cases are liable to occur: for example, it is impossible to estimate easily the composition of a slice of cake unless one knows the ingredients that were used in making it, but, even if in

the case of a few "made up" articles like this the figures taken must be to a certain extent guessed at, the total result will give valuable information as to the approximate amounts of protein, fat and carbohydrate that the reader is consuming per day. We shall use this information when we come to consider the daily output of energy from the body.

We set out in this chapter to answer the question as to what food and how much of it a man should eat—and we have got merely as far as recommending the reader to find out for himself exactly what he is eating in terms of proteins, fats and carbohydrates! As yet we have given him no information to enable him to decide whether his diet is correct in either kind or amount. But we cannot do this until we know in more detail the uses to which these materials are put in the body and, in particular, the extent to which each is suited for supplying the raw materials and energy that the body needs. To these topics we must now address ourselves, but meanwhile it will be realised that even if we have in this way postponed the final answer to our main question we have already made some advance towards it by becoming acquainted with the composition of our foods. Apart from a few articles such as sugar and suet we do not usually buy or eat lumps of pure carbohydrate, fat or protein. In our ordinary foods these constituents are all mixed up together and it has been necessary to get them sorted out before we could go on.

V

ENERGY

We have just learnt in a general way that our food supplies not only the material required for the growth and upkeep of the body but also the energy that the body expends for its various activities. A man is well nourished, therefore, only when his food contains, in addition to a sufficiency of the substances that are required for the maintenance of his tissues, enough of such substances as will, on combustion in the body, give him the amount of energy he needs for the performance of his daily work, and for the maintenance of his body temperature, without it being necessary for him to draw upon any reserve materials that he may have stored up within himself. In other words, for an adequate study of diet we must know not merely the material composition of the food-stuffs; we must investigate their energy-yielding powers as well. "Energy" is a word that is in daily use with most of us, and yet how many of us would find it difficult to explain exactly what we mean when we use it! We say we feel energetic when we feel capable of doing a lot of work, and if by this we mean physical muscular work, then we are using the word in its correct sense. For according to the standard definition energy is the power for doing work. A red-hot body, for example, possesses energy because its heat could be used to drive a suitable heat engine, and so be made to produce me-

chanical work, and we could measure the amount of heat energy that is so utilised by the amount of mechanical work that is performed. In this case we see heat energy being converted into mechanical energy, but we are just as familiar with the reverse of this process, for mechanical energy is very easily converted into heat. Such a transformation, for example, takes place whenever movement is brought about against frictional resistance. To take a particular instance, think of all the energy one expends in riding a bicycle along even a level road. During the ride one produces, maybe, a very considerable amount of mechanical energy by means of one's muscles, but at the end of the ride there is not a trace of this energy remaining in the machine, for this possesses no more capability for doing work of its own accord than it had at the outset. What then has become of all the energy that the rider has expended? It has all been converted into heat by the friction between the moving parts at the bearings of the machine, and between the rider's body and the air. A little reflection will at once convince the reader that this example is but one of a very large number of similar cases of which he could think in which mechanical energy is, as we say, "degraded" into heat and so lost. It is what is happening now at this moment with the muscular energy that I am using in writing these words: it is all being transformed into heat by the friction between my pen and the paper over which it moves, and so is escaping for ever from my control. But not, I hope, without leaving some kind of trace that will serve to stimulate some unknown reader to an interest in the things of which I write.

To resume our main line of argument: very careful experiments have shown that whenever energy is converted from one form to another the amount of this second form obtained is always an exact equivalent of the amount of the first form used. If in any kind of engine we use a certain

amount of heat energy it will always yield the same fixed amount of mechanical work, and if this mechanical energy be degraded back into heat—provided always, of course, that our apparatus has been sufficiently good to prevent loss of energy by mere wastage—we shall obtain exactly the same amount of heat as that which the engine first used. And what is true of the mutual interconversion of mechanical energy and heat is true quite generally of the transformations of all other forms of energy. This important and fundamental generalisation is referred to as the principle of the *conservation of energy,* which, put briefly, states that during these transformations energy can be neither created nor destroyed. Provided we work—or could work—with perfect apparatus so that none of the energy escapes our measurement, none of it just merely disappears; but at the same time no matter through what steps we may change from one form to the other we cannot devise any method whereby we can cause our original stock of energy to increase of itself. In order to make quite certain that our meaning is clear, let us express this in another way by saying that it is as if the rate of exchange between all the forms of energy is absolutely stable so that no amount of gambling on the energy market can ever suddenly create for us a wealth of energy that we have not duly earned. But at the same time we can be absolutely certain that no matter in what units we may measure a quantity of energy—whether we measure it as heat, as electrical energy or as mechanical energy—provided our instruments are all equal to the task we can be fully confident of obtaining a fair measure of its amount.

Now seeing that all other forms of energy tend so readily to be degraded into heat, it is easy to understand that it has been found convenient for very many purposes, particularly in dealing with the chemistry of the body, to express all the other forms of energy we encounter—the mechanical

energy of the muscles and the chemical energy of the food and so on—in terms of heat units. We must therefore give a little further consideration to the way in which heat energy is measured. If we allow a piece of some material to take up heat its temperature rises by a certain number of degrees. If now we have two exactly similar pieces of the same material and wish to heat these through the same range of temperature it is evident that we shall require just twice as much heat in order to do it as when we used only one of the pieces. We therefore agree to take as our unit quantity of heat that amount of heat which is required to raise the temperature of a fixed amount of a standard substance by just one degree. As pure water is taken as the standard substance in so many physical measurements we use it in this case also, and as scientists always use the metric system of measurement, we take one gram as the standard amount. For temperature interval we choose one degree on the Centigrade scale (which is the one universally adopted in scientific work), and finally, as the properties of water are not quite the same at all temperatures, we choose one particular degree interval—that from 15 to 16 degrees—for the purpose of defining our unit quantity of heat. So finally we have it that the unit quantity of heat is that amount of heat which is required to raise the temperature of 1 gram of pure water from 15° to 16° Centigrade. This unit is called a *calorie*—a name that is taken directly from the Latin *calor,* meaning heat. Now, while this heat unit is a convenient one for the purposes of most physical and chemical work, for biochemical experiments in which we are dealing with the total energy production of a man over a period of twenty-four hours it is inconveniently small, so that the biochemist uses a unit 1,000 times as large, which he calls the large calorie or *kilogram calorie*. It is the amount of heat

that is necessary for raising the temperature of 1000 grams (1 kilogram)—or in liquid measure 1 litre (about 1¾ pints)—of pure water from 15° to 16° C. When, therefore, in our future discussions we give the total energy production of a man as a certain number of calories it will be understood that it is to these large calories that we refer.

When we have to deal with a process in which heat is set free quickly we can measure the amount of that heat quite simply by allowing it to be taken up by a known weight of water and noting the rise of temperature that is produced. As the whole experiment takes only such a short time for its performance very little heat will have a chance of leaking away—particularly if we use a suitably insulated vessel—and so our measurement will be exact. A heat-insulated vessel arranged for the purpose of such a measurement is called a "calorie measurer" or *calorimeter*. This is the principle that is used for the measurement of the total amount of heat obtainable by combustion from a given weight of a food-stuff. The material is placed in a metal vessel immersed in a known weight of water and filled with compressed oxygen: the combustion is started most conveniently by means of an electric current, and once started proceeds rapidly, and the heat generated is taken up by the water whose rise of temperature is noted by means of an accurate thermometer. Of course we have to allow for that portion of the heat that goes to warming the metal vessel itself. As this container has to be strongly made in order not to be burst by the pressure set up inside it the whole apparatus is usually known as the "bomb" calorimeter.

Now, as we have said, in order to determine the total amount of energy that can be got from a certain quantity of any given material all we have to do is to take a sample of it, to burn it up in this bomb calorimeter and to note the

amount of heat that is liberated. When we do this with some common constituents of foods we find that:

1 gm. of protein gives us (on an average)	5.6	large calories
1 gm. of carbohydrate gives us	4.1	" "
1 gm. of fat gives us	9.3	" "

But if the reader has followed our advice and by weighing his food has found out how much protein, fat and carbohydrate he is eating per day, he will probably be more interested in the amounts of energy to be obtained from an ounce rather than from a gram of each of these food constituents. As an ounce is 28.36 grams all that is necessary is to multiply these figures by 28.36. We then find that:

1 oz. of protein yields	159	large calories
1 oz. of carbohydrate yields	116	" "
1 oz. of fat yields	264	" "

By using these figures it is easy to calculate the amount of energy obtainable from any particular diet. But before we can be certain that the same amount of energy could be obtained from this diet in the body we must consider one or two further circumstances. We must make due allowance for the possibility that these substances may not be burnt up so completely in the body as in a fire and—more important still—we must go on to ask whether the same energy relationships obtain in the body as in the fire, that is to say whether the combustion of a given amount of a substance in the body gives rise not only to the same ultimate products but also to the same amount of energy as in the fire. If we burn a certain amount of sugar, for example, in the body, will it give us the same amount of energy as if it were burnt in the bomb calorimeter?—or more?—or less? Perhaps we may be allowed to anticipate a little by saying that the amounts of energy are found by careful experiments to be the same in the two cases. The importance of this statement may

not at first strike the reader—he might almost have expected this to be the case—nevertheless the structure of living matter is so complicated and its properties are so unique that when one considers a little it would not have been so very surprising if perhaps the living body had been able to extract a little more energy from a chemical reaction than could be got from it in a dead apparatus. However, it is not so; but as the methods and equipment required to prove this statement are very elaborate and complicated we shall give them a whole chapter to themselves.

VI

THE HUMAN MACHINE

At the end of the last chapter we left the reader confronted with the important idea that the amount of energy obtainable by the burning of a certain amount of any given food-stuff in the body is the same as that which could be obtained by the combustion of the same stuff in a non-living apparatus, and we promised to explain in this chapter how this statement has been proved. What has to be done sounds easy when expressed in a few words: it is simply to give a man for a period a diet of which the total energy content has been determined by the burning of known samples in the bomb calorimeter and to measure the total energy that the man produces during this period. Then, allowing for the small amount of energy that can still be obtained by burning the excreta, and which therefore the body has not used, we make a comparison between the two quantities of energy—to see whether they are, as nearly as we can measure them, equal. The method of determining the total energy content of the food, and that also of the excreta of the subject, will be already familiar to the reader who followed our description of the bomb calorimeter in the last chapter. It is the heat production of the man himself that requires such elaborate apparatus for its measurement. The difficulty is that while in the bomb calorimeter the heat of combustion is set free very rapidly so that it can be taken

up by a known weight of water and measured before it has had time to leak away, the heat produced by the man is given off continuously over the whole period of the experiment and so cannot be collected and measured in the same way. And further, the construction of a calorimeter in which a man can live a reasonably comfortable life for days or even weeks at a time is not one of the simplest of technical problems. It is difficult enough to construct an air-tight box capable of containing a man but when it has to be heat-tight as well the difficulties are increased manyfold.

Some of the earlier experimenters on this subject, such as Lavoisier, for example, attempted to overcome the difficulties of these measurements by an instrument which, after all, embodies many of the principles of those in use at the present time. They employed what is known as the ice calorimeter. In order to measure the heat output of a smallish animal, such as a rabbit or guinea pig, they placed the animal in a vessel surrounded by ice: the heat given off by its body melted some of the ice and the water so produced was collected and measured. As the number of calories required to melt a given weight of ice was well known, it was easy from such an experiment to calculate the amount of heat given off from the animal during the period of observation. The important point about the technique of these experimenters was that in order to prevent the passage of heat into the calorimeter from the outside they adopted the ingenious plan of surrounding the whole instrument with an outer vessel also filled with ice; that is, they kept the calorimeter in an enclosure at the same temperature as itself, so that there was no exchange of heat between it and its surroundings. The reader will see the importance of this principle when we describe the calorimeter used for experiments on man. Of course it is not very practicable to construct an ice calorimeter capable of containing a man, and even if it

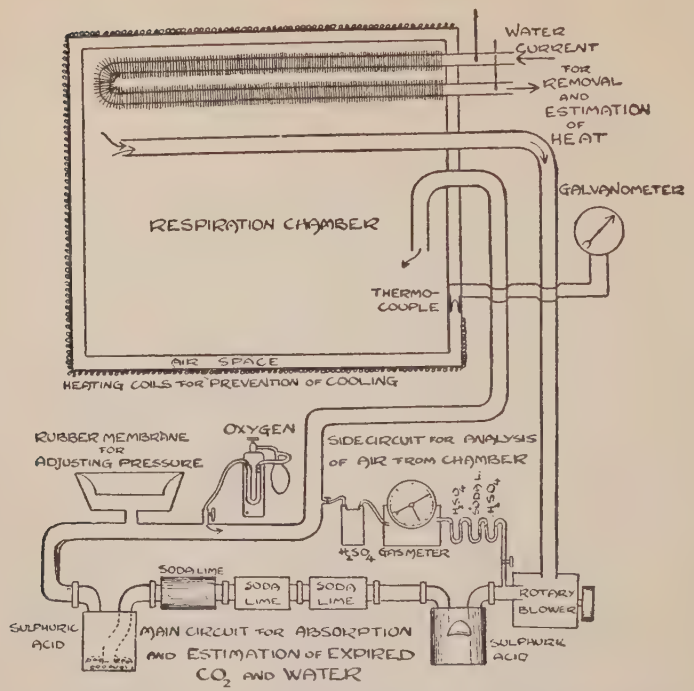


FIGURE 2. Diagram of the Atwater-Benedict Respiration Calorimeter. (Drawn from the figures and descriptions of Benedict and Milner.)

Courtesy of Messrs. Heffer and Sons.

were, it would probably be somewhat difficult to obtain volunteers to act as subjects for the experiments, except among Eskimos and such hardy folk. And in any case the disadvantage would remain that the exposure to these uncongenial arctic conditions would be abnormal for anyone who is accustomed to live in something more civilised than an iglu.

Nevertheless the principle of surrounding the calorimeter with an outer jacket at the same temperature as it-

self and of preventing by this means all exchange of heat between the calorimeter and its surroundings is a valuable one and is, in fact, that employed in the famous calorimeter first constructed at Middletown, Connecticut, by Atwater and Benedict and now re-installed in Boston. In this case the calorimeter itself consists of a large room in which a man can live for several weeks at a time. This room is enclosed in a somewhat larger chamber and any difference of temperature between the outer wall of the calorimeter and the inner wall of the enclosing chamber is registered by means of extremely delicate electrical instruments known as *thermopiles*. When the observer notices from these instruments that such a difference of temperature exists he can at once eliminate it by increasing or diminishing, as the case may require, an electric current that is made to pass through heaters in the wall of the outer chamber. We thus have an arrangement whereby all passage of heat between the calorimeter and its surroundings is prevented—or, more strictly speaking, compensated. Of course with this arrangement alone the heat liberated by the man would continuously accumulate in the chamber and this would get hotter and hotter. In order, however, to carry away this heat and at the same time to obtain a measure of its amount, radiator pipes are provided inside the calorimeter and through these a stream of cold water is circulated. The temperature of the water entering the calorimeter is carefully measured; so is that of the water leaving the calorimeter; the rate of flow of the water is also carefully controlled and measured, so that we can say that in a given time a known amount of water has had its temperature raised by a known number of degrees Centigrade, and therefore can obtain by a simple multiplication the total number of calories produced in the time of the observation. This method of measuring a quantity of heat that is evolved

slowly over a considerable period of time is known as the method of *continuous flow.*

But we have not yet described all of the essential parts of the apparatus. Provision must be made for the supply of fresh air to the man confined within the chamber. For this purpose a whole circuit of apparatus is required. The air is sucked from the calorimeter by means of a suitable rotary pump, and is then sent through absorbing vessels containing strong sulphuric acid which absorbs the excess of water vapour. Next it passes through further absorbers containing soda-lime—a porous mixture of caustic soda and lime which absorbs carbon dioxide very efficiently because the soda is spread out and distributed over the very large surface presented by the lime. Thus the carbon dioxide and water vapour produced by the man are removed from the air current. But we not only purify the air by this means. We use these absorbers to determine the rate at which the man is producing these products of combustion by weighing the separate absorbers at noted time intervals. It is of course necessary also to supply oxygen to the air current in such amount as is required to replace that which the subject uses up. This is done from a cylinder of the compressed gas communicating with the return pipe from the absorbers to the chamber, and the rate at which the oxygen is used is determined by weighing the cylinder from time to time.

These are now the main features of this extensive apparatus which, it will be seen, is really quite simple in principle. It is merely its size that makes it expensive to instal and somewhat difficult to run. There are, however, one or two other details which we might mention, though they do not concern us very much. In order to control the composition of the air in the chamber and so to make certain that the main

absorbers are acting efficiently, a small circuit composed of a chain of miniature absorbers and a gas meter is provided: these make it possible to estimate the amount of water vapour and carbon dioxide in a known volume of the air that is being supplied to the man. Then as the whole rigid apparatus is closed air-tight during the prolonged experiment it is necessary to provide some place where there will be a certain amount of "give" in order to compensate for changes in the prevailing barometric pressure; otherwise quite considerable stresses might be set up and these would lead to leaks if to no more serious consequences. Such a flexible point or pressure equaliser is provided by connecting with the air circuit a pan closed with a large rubber bathing-cap which will expand or collapse according to the relation of the pressures inside and outside the apparatus. Of course we need hardly mention that the chamber must be provided with air-tight "locks" for the introduction of food and removal of excreta, with a bed and the essential articles of furniture, and a telephone with which the subject may remain in touch with the outside world.

And then lastly there must be some provision whereby the subject may obtain muscular exercise, not merely in order to keep fit, but chiefly because it is desired to carry out these observations not only on resting individuals but also on persons carrying out muscular work of various intensities. To this end there is placed in the chamber a stationary bicycle mounted up off the ground on a wooden stand and arranged so that its back wheel works against a frictional or other brake. In this way the mechanical work performed by the subject as he carries out his cheerless pedaling is all converted into heat (as described in the previous chapter) and so is included in the total energy output and measured along with the heat produced directly by the subject.

But what, you ask, was found out when all this elaborate machinery was finally completed and its human occupant took up his abode in the solitary cell? This information can be given in far fewer words than it took to describe the method whereby it was obtained. All the energy entering the chamber in the form of food during a given time was reckoned up; so was that leaving the chamber during the same time. This was, of course, mostly in the form of heat produced by the subject, but a small amount of it was that still contained in the fæces and urine produced during the experimental period, and measurable in the bomb calorimeter after previous evaporation of these materials to dryness. And when these two total quantities of energy were compared it was found that they were exactly equal. Or rather, to speak the truth, *almost* exactly equal. For even the most careful of scientific measurements are never *absolutely* exact. Small unavoidable errors creep unobserved even into our most painstaking work. There is a limit to the responsiveness of even the most delicate measuring instrument. And in the case of the calorimeter we have been considering it will be easily understood that tiny little losses of matter or energy might easily go unnoticed. But what we can say is that *as accurately as they could be measured* the ingoing and outgoing amounts of energy were equal. As a matter of fact the accuracy of these measurements was really very great. During a whole series of experiments 592,880 calories went into the chamber and 593,381 were removed, so that the fraction unaccounted for amounts to only 501 calories, that is, less than 0.1 per cent of the whole.

Now this is a very important result indeed. It means that a man cannot obtain the smallest fraction of energy otherwise than by the combustion of the materials he takes in as food, for if he could we should expect to find more energy coming out of that calorimeter chamber than went in. But

such was not the case. We must conclude therefore that the human machine has no undiscovered source of physical power: it cannot create energy where none existed before: it can merely transform the chemical energy of the food into the mechanical and heat energy of the body, and the laws governing these transformations are shown, by the experiments we have just described, to be the same as those governing similar transformations in systems where life is not concerned. The law of the conservation of energy circumscribes our throbbing lives just so inevitably as it controls the upheavals and transformations of the dead earth whence we arose and whither we return. So that just as we find no need to assume the existence of a special "vital force" for the elaboration of the particular organic substances that occur in living organisms (see page 112) so too we find no need to postulate any such mystical vital force when we study the energy exchanges of the body.

But this result is not merely of great philosophical interest in the sense that it must be taken into account in any attempt to decide man's relation to the universe as a whole: the conclusion to which it brings us has a very practical bearing on the more material question as to how much food a man should eat per day. For seeing that a man has available only that amount of energy which he can get by the combustion of his food materials, it is evident that if we know the amount and kind of food he is utilising we can calculate how much energy he can expend; or, *vice versa,* if we know the amount of energy that he expends we can calculate the amounts of particular food materials required to supply it. Now Atwater and Benedict's experiments were carried out on subjects in all degrees of activity ranging from complete rest to the severest muscular work that the man could do on the bicycle. They therefore give us information as to the amounts of energy that the human

body does actually put out per day under these various conditions.

With regard to this it must be mentioned in the first place that even when the body is nominally at rest it is using a quite appreciable amount of energy. For the maintenance of life requires the uninterrupted carrying on of certain activities even though the subject is not producing any external work. For example, the heart can never relinquish for a single moment during life its duty of pumping the blood round the body for the purpose of carrying to the various organs the materials they require for their activities and carrying from them the waste products that they produce. Then again the chest and other muscles concerned in breathing must function continuously in order to supply to the body the oxygen it needs and to remove from it the carbon dioxide it forms. The alimentary canal—the stomach and intestine—is always active to a greater or less extend in the digestion of food and the absorption of nourishment. And lastly energy is required for the maintenance of the body warmth.

These activities, which, it will be noticed, are all involuntary and are carried out in our bodies in the absence of or even in spite of any conscious intervention on our part, are the chief of those which *must* go on without pause in order that life shall continue, and the energy necessary for the carrying out of these fundamental activities represents the minimum amount of energy that the body *must* expend in order merely to remain alive. It is the amount of fuel consumption that must take place in order, so to speak, to keep the engine just turning over, but ready to spring into vigorous activity as soon as the need or the stimulus thereto arises. This resting energy consumption is called the *basal metabolism*. Metabolism (Gr. μεταβολή = a change) is a word used in biochemistry to mean all that collection of

processes in living matter whereby substances are changed chemically into other substances. In this case the particular change we are considering is the combustion of energy-yielding fuel. We refer to the rate at which this process goes on under conditions of bodily rest as "basal" because it furnishes us with a base line from which to reckon when we wish to consider the energy used over and above this amount while the body performs external work. Naturally the actual value we obtain for this base line for any given person will depend on a number of factors, such as our success in restraining him from performing voluntary movements of all kinds, and the extent to which we reduce the heat loss from his body. If a man who has received no food for some hours, and who therefore is not carrying out much digestive work, remains as quiet as is humanly possible in a comfortably warmed atmosphere, he will expend about 1,700 calories of energy in the twenty-four hours, but such a low figure is obtained only when these rather special precautions are taken. Under more ordinary circumstances, when the man is lying down at rest in a room at ordinary temperature, his energy exchange during 24 hours may easily amount to 2,600 calories—almost 1,000 calories more than the barest minimum. When on the other hand he is carrying out the severest muscular work of which he is capable—when he is out to establish a record—his daily energy turnover might well amount to something like 9,000 calories.

Now this information gives us the first indication of a definite answer to the question that initiated the whole of this present discussion, namely the question as to the amount of food an individual requires per day. We now see that if he is engaged on sedentary tasks such an amount of food as would supply him with about 3,000 calories daily would be sufficient; if he is carrying out really hard physical work he will require at least 7,000 calories a day; and in other

cases he will need an intermediate amount of energy according to the actual severity of the work he performs. It is interesting and important to note that according to the results obtained by Atwater and Benedict, mental work, such as the solving of complicated mathematical problems or the reading of foreign languages, does not lead to any detectable increase in the metabolism and so does not call for an extra ration of food above the basal amount.

In most cases, however, it is hardly possible to take a man and arrange for him to carry out his ordinary daily work inside a calorimeter, particularly when that work is of the heavy muscular type. We could hardly enclose a working bricklayer or blacksmith in such an apparatus. But relying on the applicability of the law of the conservation of energy to living matter in general and to the human machine in particular we can calculate the daily energy output if, from an analysis of the air he expires, we determine the amounts of the various substances he is burning in his body in order to produce that energy. As such a calculation involves principles with which we have not yet dealt we will devote a separate chapter to this part of our discussion.

VII

THE LIVING FIRE

Now that we have shown that the energy expended by the body is exactly equal to that which, in any case, could be obtained by the combustion in a fire of the food the body uses, we can continue our study of the energy use of the body by considering the amount of fuel it burns up under various conditions, obtaining our information as to the amounts of material burned from the quantities of the products of combustion formed. This is, I believe we said, by far the easier way of investigating this problem, for it is far less difficult to construct a chamber or apparatus that shall be gas-tight, and so suitable for the measurement of the oxygen a man consumes and the carbon dioxide he produces, than it is to make it heat-tight and so to measure his energy output directly. In fact an apparatus for the measurement of this "total respiratory gaseous exchange" of a man may be relatively simple. All we want is a large air-tight box in which he can be placed while a current of air passes in at one end and out at the other. This current of air must be measured by means of an accurate gas meter, and the amount of oxygen it loses and the amount of carbon dioxide it gains as it passes through the chamber must be determined by careful analysis of the ingoing and outgoing air. In the case of a hospital patient (and it is obviously of great value to be able to find out by this means how brightly the

fire of a sick man's life is burning) the box may be made so that it encloses the bed. For use with animals the apparatus is still easier to construct as it can be made of smaller size.

But when we are working with a human subject we do not even require the air-tight box except for the most accurate experiments. As practically all but the smallest traces of the oxygen he uses and of the carbon dioxide he produces pass in or out of him, as the case may be, through his lungs (the tiniest fraction only diffusing through the skin) we need only to get the person under test to breathe into a suitable apparatus for the measurement and analysis of his expired air. A mask may be provided for collecting this expired air, but it is usually easier to collect it without loss by closing his nose with a clip and getting him to breathe through a tube in his mouth. In either case we must provide suitable valves so arranged that when he inspires air passes in from the outside, while when he expires none of the air he gives out leaks back to the outside atmosphere but all passes on to the measuring and analysis apparatus. In the case of active outdoor exercise (which appeals more to most of us than work on the stationary bicycle) the apparatus can be made so that gas meter and all can be carried on the subject's back. Or the subject may carry a large air-tight bag made of canvas and lined with indiarubber, and provided with a large tap through which he breathes into the bag and by means of which he closes it when the air expired over a given period is collected. The composition of this gas is then determined by analysis, and its volume is measured by passing it through a gas meter, when the bag is brought back to the laboratory.

For determinations on patients who can sit up and cooperate there have been devised various convenient forms of recording apparatus in which the breath is collected in some kind of gas holder fitted with a little writing point by means

of which the height at which the holder stands, and hence the amount of gas it contains, can be recorded on a moving strip of paper. In this form of apparatus—which is much used for investigations on hospital patients—a large vessel of soda lime is fitted inside the gas holder. This latter is filled with oxygen at the start and as the patient breathes in and out of the apparatus (no valves are necessary for this —only a nose clip and a mouth-piece are required) the carbon dioxide he produces is absorbed by the soda lime, while the gradual sinking of the gas holder indicates the rate at which his body is using the oxygen. The record of course shows not only this gradual fall but also the up-and-down movements of the spirometer gas holder due to the individual breaths and so gives us information as to the rate and depth of the breathing. We obtain in this way information only as to the rate at which the man is using oxygen, but as will be clear to the reader from what follows immediately, this is sufficient to enable us to calculate the total amount of combustion going on in his body and even the total energy production, provided we know, as in general in the case of a hospital patient we do, the composition of his diet.

In the case where we do not know the composition of a man's diet and yet wish to calculate his daily energy production we must know what particular substances—carbohydrates, fats or proteins—are being burned in his body, and in order to find out something about this we must know not only the rate at which he uses oxygen but also the corresponding rate at which he is producing carbon dioxide. We shall therefore have to use one of the other types of apparatus already described as suitable for this purpose. But when we have made our actual experiment and determined thereby the oxygen usage and carbon dioxide output—in short the gaseous exchange—during a given time interval, how can we obtain from this an estimate of the total amount

of energy that he has expended in that time? From the amount of carbon dioxide he produces we can at once calculate the amount of carbon he has oxidised in that time, since the relative amounts of oxygen and carbon that go to make up carbon dioxide are well known. We know, therefore, also that amount of oxygen which has gone to the oxidation of this carbon and can therefore find by subtraction from the total quantity absorbed the amount of oxygen that has been used to form water; and hence from the known composition of water the amount of hydrogen that has been burned. We have had to argue in this somewhat roundabout fashion in order to find the amount of water produced in the body, because this is not easy to estimate directly. The amount of water given off from the body varies, of course, with the amount drunk, and further the water is got rid of from the body through so many different channels—not only as vapour from the lungs, but also as sweat from the skin and urine from the kidneys.

But even though we have in this way been able to calculate how much carbon and hydrogen have been burned up in the body we are not yet in a position to calculate directly the amount of energy that has thereby been produced. For the body does not burn carbon and hydrogen as such; it takes in and utilises these materials in the form of carbohydrates fats and proteins, and these are the substances that are ultimately burned. Now it is easy to show by means of the bomb calorimeter that when we burn a gram of carbon in the form of fat we obtain from it an amount of energy different from that which we obtain when we burn a gram of carbon in the form of sugar. This is not surprising, for the energy with which the carbon is held in chemical combination in the fat is different from that with which it is held in combination in the sugar. This chemical energy of combination appears in the total energy liberated when the substance burns, so that

the heat of combustion of a compound will usually come to be different from the sum of the heats of combustion of the total quantities of the individual elements of which that compound is formed. All this means that if we wish to calculate the energy liberated in the body it will not suffice to know merely the total amounts of carbon and hydrogen that are being burned up in it: we must know the quantities of fat, carbohydrate and protein that these amounts of carbon and hydrogen represent. For the present we will leave the proteins out of account and consider the case in which the energy-yielding substances of the diet are practically entirely composed of carbohydrates and fats so that relatively little protein is burned up and we shall make but little error if we neglect it. This being granted, the next point we wish to make is that in order to determine the amounts of fat and carbohydrate that are being burned in the body we need no further information than that which we obtain when we measure the total gaseous exchange. Here we must ask for the reader's closest attention because the argument, although perfectly straightforward, requires a little effort for its first comprehension.

Of the total oxygen used by the body part goes to the burning of carbon to carbon dioxide and the rest to the burning of hydrogen to water. Now the amount of carbon dioxide produced from a given amount of oxygen will evidently depend on two chief factors in the composition of the material being burned. It will depend firstly on the ratio in which carbon and hydrogen are combined in the fuel material, for evidently the more hydrogen, relatively speaking, the greater the proportion of the oxygen that will be used to burn this to water, and the smaller therefore the proportion that will be left for the formation of carbon dioxide. So that if we had a number of substances containing various proportions of carbon and hydrogen we could, by observing

the amount of carbon dioxide produced for a given amount of oxygen used during their combustion, determine the relative proportions in which carbon and hydrogen are present in the different substances, and, if necessary, could use this information for determining which particular substance was being burned in any given case.

But the substances—fats and carbohydrates—that constitute the fuels of the body contain not only carbon and hydrogen but combined oxygen as well, as part of their composition, and this brings us to the second of the factors that determine the amount of carbon dioxide produced for a given amount of oxygen used. For evidently the more oxygen already combined in the substance to be burned the less need be supplied from the outside in order to convert all the carbon to carbon dioxide and all the hydrogen to water. We might interpolate here that the reason why explosives such as gunpowder, dynamite and T.N.T. can burn up so instantaneously in a closed space is that these materials contain combined within themselves enough oxygen to burn up all their carbon, hydrogen and other combustible constituents, and so are independent of a supply from the outside. To return, however, from this digression: It is merely a matter of chemical analysis to show that a carbohydrate contains relatively much combined oxygen and a fat very little. This means that practically all the oxygen required for the burning of a fat in the body must be obtained from the inspired air, and furthermore the oxygen is shared between the carbon and hydrogen so that only a certain proportion of it goes to form carbon dioxide (the rest being used to form water with the hydrogen). Now when we bear in mind the well-established fact that when a given volume of oxygen combines with carbon to form carbon dioxide we obtain just the same volume of carbon dioxide as we took of oxygen at the beginning, we at once see that during the combustion of a fat,

whether in the body or outside it, the amount of carbon dioxide produced must be considerably less than the total amount of oxygen used for the combustion. In other words when fat alone is being oxidised in the body the amount of carbon dioxide given out to the expired air is less than the total amount of oxygen absorbed, during the same time of course, from the inspired air. The ratio

$$\frac{\text{total carbon dioxide produced}}{\text{total oxygen absorbed}}$$

is therefore less than 1. Actually for a fat this ratio comes to have a value of about 0.7, which means that of any given amount of oxygen used for the combustion of a fat rather less than ¾ goes to the burning of carbon, more than ¼ being used for the burning of hydrogen.

On the other hand, carbohydrates, as we said, contain a relatively large proportion of combined oxygen—enough, in fact, to unite with all the hydrogen to form water (see p. 40), so that when we burn a carbohydrate it is necessary to supply only enough oxygen from the outside to convert all the carbon to carbon dioxide. In other words for a given volume of oxygen supplied from outside an equal volume of carbon dioxide will be produced, so that for the combustion of a carbohydrate the ratio

$$\frac{\text{total carbon dioxide produced}}{\text{total oxygen taken in}}$$

will be exactly equal to 1.

If a mixture of fats and carbohydrates is burned the value of the ratio will of course come to something between 0.7 and 1 according to the proportions in which the fats and carbohydrates are being utilised. If there is a greater proportion of fat the value will be correspondingly nearer 0.7;

if a preponderance of carbohydrate, then the value will the more nearly approach unity. It will thus be seen that this ratio of the volume of carbon dioxide produced to the volume of oxygen utilised in a given time is of very great importance in the study of metabolism inasmuch as it furnishes information as to the particular substances that are being burned in the body: it is therefore given the special name of *respiratory quotient.* If we have the value of the respiratory quotient we can easily calculate by simple proportion the ratios in which fat and carbohydrates are being used as fuel in the body, and the value of the quotient itself is readily obtained by a little calculation from the results of the measurement of the total respiratory exchange. The total amount of carbon dioxide produced tells us the total amount of carbon oxidised, the value of the respiratory quotient gives us the ratio in which fats and carbohydrates are being utilised, and so enables us to divide up the total combustion between these two forms of fuel. Then, as we know the amount of energy to be obtained by the combustion of a gram of each, we can add up the total energy production of the body.

Now in this argument so far we have pretended that the body has been burning only carbohydrates and fats. But proteins make up a considerable part of an ordinary diet so that they also come to be used as fuel in the body. What, then, of a respiratory quotient for them? From the average composition of various proteins we can quite easily calculate the amount of oxygen required for burning their carbon and hydrogen, and also the amount of carbon dioxide that would be produced, just as we did for the other fuel materials—and from these figures we find that the respiratory quotient for a protein comes to be about .85. But this is a number that we do not use so often as the corresponding values for fat and carbohydrate because, for

the sake of simplicity, when we carry out an experiment to determine the total gaseous exchange of an individual during the performance of a set amount of muscular work, we take him at a time when he is not using much protein —that is, several hours after his last meal. The most convenient thing is to get him to do the work in the morning before breakfast. At that time not only will all the protein that he has eaten during the previous day have been digested, but its nitrogen will have been got rid of as nitrogenous compounds in the urine, leaving the combustible residue to be stored mainly as carbohydrate. We shall explain this process of nitrogen elimination more fully in a later chapter; all we wish to emphasise at the moment is that if we take an individual sufficiently long after his last meal and get him to carry out a piece of muscular work, the fuel he uses for the carrying out of that work will be practically all carbohydrate and fat, and we shall make very little error if we neglect the protein altogether. This is what is usually done, but in cases where the highest accuracy is required we should have to estimate the total amount of nitrogen in the urine formed during the period of the work and to include in our calculation the (small) amount of protein that this represents. It comes to this: that those of us who from choice or necessity are addicted to the pernicious habit of "working between meals" run on a mixture of all three fuels—carbohydrate, fat and protein—but, in order to make our experiments more simple, we can get the body to run on a mixture of fat and carbohydrate alone.

By collecting and measuring and analysing the expired air of an individual during a given period of time we can, then, determine the amount of each of these fuels consumed in his body during the performance of the work, and as we know the amount of energy obtainable by the combustion of each fuel, we can work out the total amount of energy the

person requires during the measured time interval. The wearing of a mask or a nose-clip and mouth-piece for the purpose occasions no great inconvenience. When we do this with a man in a completely resting condition in comfortably warmed surroundings we find that he uses up about 1,700 calories in 24 hours for the absolutely essential processes of his body and the maintenance of his temperature. This, as we explained on page 75, is the basal rate of metabolism below which his life cannot be permanently maintained at all. Every movement he makes and every draught of cold air to which he is exposed will require the expenditure of a corresponding amount of extra energy over and above this minimum amount. It is estimated that the mere fact of being "up and about" increases the metabolic rate by 10 per cent of its basal value, and as one is up and about for roughly 16 hours out of the 24 this means an increase of something like 120 calories per day. Then there is the energy to provide for the minor activities of the day, such as dressing and undressing, moving about the room, and so on. These would probably use up about 200 calories a day so that we arrive at a total of 2,020 calories a day for an individual who remains at home and does not do any muscular work. But most of us have to travel a greater or shorter distance to and from our places of work and this travelling itself would on an average require about 300 calories so that the sedentary brain worker employed away from his home will require 2,320 calories of energy per day in order to meet his requirements. We shall therefore not be far wrong if, making an allowance for the fraction of his food he does not digest and so loses in the fæces, we give him a daily food ration capable of yielding about 2,500 calories. But it must be realised that this is by no means a fixed estimate and that the amount of energy supplied must be increased in accordance with the severity of the climate to which the man is exposed

and also with the size of the bodily frame that he has to maintain. But of this more later.

If now instead of dealing with such a brain worker we deal with a man who earns his living with his hands, we must allow him a still further ration of energy-yielding food in order to provide the energy he expends during the muscular efforts of his daily work. Experiments have been performed on individuals engaged in a great variety of useful and other occupations and we now know how much extra energy is necessary for the carrying on of an hour of these different activities. Some of the results so obtained are collected in the following table, and by their aid, if we know the num-

EXTRA ENERGY USED PER HOUR IN VARIOUS OCCUPATIONS
(quoted from Lusk)

Men's Occupations	*Extra Calories used per hour*
Tailor	44
Bookbinder	81
Shoemaker	90
Metal worker, filing and hammering	141
Painter of furniture	145
Carpenter making a table	164
Stonemason chiseling tombstone	300
Man sawing wood	378
Women's Occupations	
Seamstress, needlework	6
Typist, 50 words a minute	24
Seamstress, using sewing machine	57
Bookbinder	63
Housemaid, moderate work	81
Laundress, moderate work	124
Housemaid, hard work	157
Laundress, hard work	214

ber of hours a day that an individual spends in any of these occupations, we can at once calculate the amount of energy he expends on the work.

If we work out from data such as these the amount of energy expended by any individual on his work, and add to this the amount of energy required for his resting needs, we obtain the total amount of energy that the individual uses per day. We have already seen that a sedentary home worker (such as an author) expends not much more than 2,000 calories, all told, in the 24 hours: by a similar argument we find that a worker in an office uses between 2,500 and 3,000 calories; and that a day of moderately heavy work, such as gardening, involves an expenditure of up to 4,000 calories; really hard muscular work would bring the figure up to 5,000 calories; while the record seems to be held by lumbermen, who are doing the very hardest of muscular work, under outdoor conditions and whose energy output seems to be between 8,000 and 9,000 calories a day.

Now these results are of fundamental importance in the study of diet for they enable us at last to give an answer to the question that has for so long been before us, namely, "how much food does a given individual require per day?" For seeing that a man has no source of energy except that which he can obtain by the combustion of the fuel materials contained in his food the first requirement of a suitable diet for him must be that it shall provide him with enough calories to supply all the energy he uses during his daily occupations. In order to determine whether his food is adequate he must first decide whether his work is light, moderate or heavy, so far as muscular effort is concerned. This will tell him whether he requires three or four or five thousand calories a day. He must then carefully weigh his food and from the table on pages 54 and 55 find out how much of protein, carbohydrate and fat he is eating per day; then, knowing the

number of calories obtainable from each gram or each ounce of each of these fuel materials, he must add up the total number of calories he is receiving per day, and make sure that they are at least equal to his estimated daily energy expenditure.

But before the reader actually embarks on such an estimation there are one or two further points he should be made aware of. In the first place we should mention that, although in our experiments we can for simplicity arrange for the body to run practically entirely on carbohydrates and fats, under ordinary circumstances each one of us derives a very considerable fraction of his daily energy ration from proteins, so that there must, of course, be no question of not including them when adding up the energy content of the diet. Secondly, there is an important point that we have not yet mentioned about the energy yielded by proteins in the body. In the bomb calorimeter we saw that proteins give off 5.6 calories per gram. But in the body the combustion of proteins is not quite so complete as in the calorimeter. In the calorimeter all the carbon of the protein is burned to carbon dioxide and all the hydrogen to water, but in the body a certain amount of the carbon and hydrogen of the protein goes to form the substance *urea* which is got rid of in the urine. In this way a fraction of the combustible material of the food proteins is wasted from the body and instead of obtaining 5.6 calories from each gram of protein the body obtains only 4.1 calories, or from each ounce only 116 calories. This then is the figure we must use when we are calculating the share of our total daily energy ration that is contributed by the proteins of our food. In the case of carbohydrates and fats a similar consideration does not arise as the combustion of these materials in the body is normally just as complete as in the bomb calorimeter, so that the same amount of energy is obtained in either case. Let us collect

the numbers again for the sake of convenience. We can say that *in the body*

protein	yields	4.1	calories	per	gram	or	116	calories	per	ounce
carbohydrate	"	4.1	"	"	"	"	116	"	"	"
fat	"	9.3	"	"	"	"	264	"	"	"

It will thus be seen that an ounce of protein yields the body only the same amount of energy as an ounce of carbohydrate, although it is much more expensive to buy.

We can consider the constituents of food in their three main groups in this way because the individual members of each group differ very little among themselves with regard to energy-yielding power, and because from the point of view of obtaining energy it matters little what particular fats or carbohydrates or, within limits, what proteins a man eats. It makes very little difference whether he prefers to get his proteins from fish rather than from meat, his starch from bread rather than from potatoes, and his fat from oil rather than from butter. In such matters he can follow his own tastes and fancies. For a reason that we shall explain when we talk about diabetes it is necessary always to include a good proportion of carbohydrate in the diet. The body cannot run on fat alone; but there are not many people who would be inclined to eat butter without bread or fat meat without vegetables.

But no matter how the diet is made up it is not possible to determine whether it is sufficient for the needs of the particular individual consuming it without a considerable amount of weighing and consulting of tables of food analyses and of calculations of calorie values. For as the reader must have gathered by this time, it is not the mere bulk of the food, nor indeed its cost, that determines its value, but its calorie content, and this cannot be estimated by mere inspec-

tion. Fortunately, however, the number of calories obtainable from 1 lb. of most of the commoner food-stuffs has been calculated once and for all, and from these results there have been worked out the amounts of some of the commoner articles of diet that yield exactly 100 calories. As this makes it so much easier to visualise the energy-yielding values of the foods, and saves such a great deal of arithmetic in the working out of diets, we shall list the more commonly-accepted data as follows:

PORTIONS OF VARIOUS FOODS YIELDING 100 CALORIES IN THE BODY

1.3 oz. bread (slice 6 × 3½ × ½ in.)
1 oz. oatmeal
1 medium-sized boiled potato (3.6 oz.)
1 shredded-wheat biscuit
2 tablespoons or 6 cubes of sugar (.9 oz.)

2 oz. lean beefsteak (slice 2 × 1½ × ¾ in.)
1 large boiled egg
1 mackerel

1 ordinary ball or pat of butter (.4 oz.)
.8 oz. cheese (1⅛ in. cube)
⅓ pint of milk

1 large apple, banana or orange
14 oz. cabbage
1½ figs
20–24 peanuts
24 raisins

These then are the broad outlines of that part of the science of nutrition which deals with the fuel requirements of the body. But there still remain a few details with which the reader must be made acquainted before he can use the in-

formation we have already given him for making up an energy balance sheet for himself and his family. For example, although the chief factor that decides an individual's energy requirements is the amount of muscular effort that he has to make during his daily occupations, there are one or two other conditions that do influence in a minor degree the amount of fuel he consumes. One of these is *size*. A man with a large frame requires a somewhat larger amount of energy per day than a smaller fellow engaged on the same job: although each may expend the same amount of energy on the work the heavily built man will have a larger basal metabolism to provide for than his more diminutive colleague. Nor is this surprising when one realises that the larger the man the larger the total area of his body and the larger the area of his body the greater the opportunity for the loss of heat; the larger therefore must be the fire he must keep going in order to maintain his body temperature. In this way it might very well come about that a 140 pound man could get on quite well with 500 calories less per day than a 180 pound man doing the same kind and amount of work.

The influence of this factor of surface becomes still more striking when we consider not human individuals but animals of very different kinds and sizes. In a mouse, for example, a very considerable portion of the body is on the surface and in any case no part can be very remote from it. The conditions for heat loss are therefore very favorable, and when we come to measure the total combustion going on in the body of a mouse it is not so surprising to find that, *per unit of body weight,* it is much higher than that of a man. If, on the other hand, we go to the other extreme and consider a large animal, such as a horse, we realise that of its tissues a very large proportion will be far from the surface and some will be so deeply embedded in the body of the beast as to be very efficiently protected against heat loss. In cor-

relation with this the heat production *per pound or kilo* of horse is small. But if in the three cases we calculate the amount of heat produced not per unit of body weight but *per unit of body surface,* then we find that it turns out to be much the same for each animal. Indeed, we might have expected that, other things being equal, the rate of heat loss from a square inch of skin might have been the same whether that skin was on the surface of a horse or a man or a mouse, seeing that the body temperatures of all of them are practically equal. If the reader will glance at the following table he will see the degree of correspondence that is actually found:

Animal	*Weight (kilograms)*	*Calories produced in 24 hours*	
		per kilo of body weight	*per square meter of body surface*
Mouse	0.018	212.0	1188
Man	64.3	32.1	1042
Horse	441	11.3	948

Doubtless the same result could be illustrated still more strikingly if we had any data concerning the rate of energy production in an elephant; but no one seems to have succeeded in getting this beast to breathe into a bag, or to have constructed a calorimeter large enough to contain him.

Now this relation between energy consumption and size is not merely interesting for its own sake; it has a very important application to the problem of the feeding of children. It will doubtless be agreed that in many respects children resemble small animals, and their behaviour so far as their energy usage is concerned furnishes no exception. Relatively speaking, a child has more surface in proportion to its weight than an adult has, so that its body loses heat correspondingly easily. Two 70 lb. children together need more

calories a day than one 140 lb. man because between them they have a greater surface. For this reason alone a child requires a larger energy ration per pound of body weight than does an adult. But in addition to this it has been proved by experiment that the basal metabolism is greater even per square foot of body surface in a child than in an adult, partly, at all events, because the processes of growth require not only raw materials for the manufacture of the new tissues but energy for their building. And then what shall we allow for the energy of the normally healthy child's all too vigorous activities? It is not easy to form a reliable estimate of the total amount of energy used by children at different ages in these various ways: we have not as many data as we should like on the subject but the following are the most trustworthy figures we have so far. They are quoted from Dr. Emmett Holt of New York who devoted many years of study to the question.

TOTAL NUMBER OF CALORIES REQUIRED PER DAY BY CHILDREN

Age (*years*)	*Boys*	*Girls*	*Age* (*years*)	*Boys*	*Girls*
1	950	940	10	2330	2195
2	1135	1110	11	2510	2520
3	1275	1230	12	2735	2864
4	1380	1300	13	3040	3210
5	1490	1410	14	3400	3330
6	1600	1520	15	3855	3235
7	1745	1660	16	4090	3160
8	1920	1815	17	3945	3060
9	2110	1990	18	3730	2950

These numbers are admittedly only rough estimates, but they will furnish a scientific explanation for the ravenous appetites of any flourishing youngsters that the reader may

happen to have occasion to observe, and will serve to remind him that it is in youth that the fires of life burn most brightly. . . .

So much for the children of the family. Our account would, however, be very incomplete did we omit all mention of their mother. It is a well-established fact that, curiously enough, women are much more economical of their calories than are either their husbands or their children—to such an extent, in fact, that a woman requires only five-sixths of the calorie ration that a man of the same size would require for the same amount of work.

The reader who has followed us so far is now in possession of all the information he requires to enable him to provide an adequate supply of energy for himself and any others for whose diet he may be responsible. The trouble of weighing up all the constituents of a day's meals occasionally is by no means great and is amply repaid by the insight it gives into one of the most fundamental of life processes. The question of the food required for the *maintenance* of the human machine (as opposed to the fuel required to run it) we shall deal with in the next chapter.

In conclusion we shall just mention a few of the effects that are liable to follow if the calorie value of the food is not suited to the requirements of the individual. Let us suppose, first, that he eats too much food. He will then store the excess in his body and as a result will grow fat. The unwanted fat of the food will (after certain changes of composition) be stored below his skin and in the fat deposits that surround many of the internal organs. Superfluous carbohydrates will be stored as glycogen in the liver and muscles, but will also help to give rise to fat in the body. This process of the conversion of carbohydrate food into fat is seen in the ordinary fattening of cattle. The animals are given so much carbohydrate food that they cannot store all the ex-

cess in that form; a very large proportion of it is therefore put down as fat. It has indeed been proved by direct chemical analysis that the body of a pig acquires during fattening much more fat than is given it in its food. Incidentally it is interesting to observe that fat is a very compact form in which to store reserve fuel for each ounce of fat gives 264

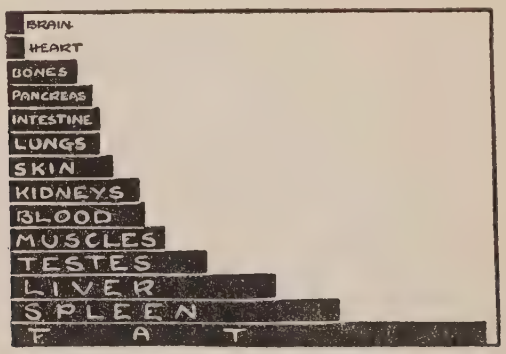


FIGURE 3. Relative loss of weight of various organs during starvation. *Courtesy of Messrs. Heffer and Sons.*

calories on combustion as opposed to only 116 calories given by an ounce of carbohydrate (page 90). The human body has no power of storing up proteins as such: if more of these substances be eaten than the body requires the unwanted nitrogen is got rid of as nitrogenous compounds in the urine, and most, at all events, of the combustible residue of the protein is stored as glycogen.

In the opposite case, when the amount of food eaten is below that required to supply the energy expended, the body has to draw upon these stored reserves. Its weight goes down and its total rate of energy production is diminished. A long period of undernutrition causes the body to become easily fatigued and inefficient although it seems not to

affect the mental powers. If the starvation is complete and no food at all is given these stores of fat and glycogen are usually sufficient to maintain life for some time, but sooner or later there comes a point at which the body has to begin to use the substance of its own tissues in order to obtain the energy necessary for the carrying on of its essential functions. When this begins to occur death is usually not long delayed. On examination of the carcass of an animal that has been starved to death it is found that the various organs have not contributed equally of their substance for use as fuel. Naturally the reserves of fat and glycogen have practically completely disappeared and the muscles may be reduced to half of their normal weight; but such important organs as the heart and brain will be practically unaffected—how little they lose can be gathered from the diagram of figure 3.

We can see a great deal of significance in this observation when we remember that the heart and brain are just the organs whose work *must* be carried on if the life of the animal is to be maintained at all. For the blood must be kept circulating in the impoverished body in order that such of the sadly diminished reserves as remain may be made available to the organs where they are of most use, and the brain must remain sufficiently active up to the end in order that the animal may be alert enough to take advantage of the smallest opportunity that might present itself for obtaining food of which it stands in such dire need. In this behaviour of the body during starvation we thus have a striking example of the way in which the various organs co-operate during a period of stress. Each is sacrificed according to the extent to which it can be spared. An organism is not a collection of independently working organs but is a unified, correlated system in which the activities of each part work for the furtherance of the life of the whole.

VIII

WEAR AND TEAR

Up to the present we have been dealing with the laws governing the production of energy in the body, and in considering this part of our subject we have treated the proteins, fats and carbohydrates of our food as being all in the same category so far as their use as fuel is concerned. No one of them was regarded as being of greater importance in this respect than any other. But now we have to deal with processes in which the proteins are more intimately concerned and in which their functions cannot be taken over by the other constituents of the diet.

The reader will probably remember how in our opening chapter we pointed out that the fabric of a living organism is far from permanent; that it is, on the contrary, subject to a continuous breaking-down process which we have referred to as "wear and tear," and that its continued existence is dependent on a never-failing supply of the materials required to make good this continuous loss. We have hinted also that the proteins play a unique part in the building up or repairing processes inasmuch as they and they alone can provide the necessary nitrogenous materials from which new living matter can be made. It comes to this: that the body like every other machine must receive occasional spare parts for the maintenance of its fabric, and it is our object, in the present chapter, at least to begin some account of the way in which these spare parts are provided.

In the first place the question naturally arises—How do we know that the living machine is really all the time slowly disintegrating? In the case of an ordinary non-living machine we can quite easily recognise the process. We find the various moving parts more or less worn after a certain amount of use, some of them perhaps entirely missing, and we know that the future activities of the machine will be seriously impaired if these are not replaced. What of the living machine? In this case it is an impairment of chemical structure that we must seek, so that our problem is one for the biochemist to investigate.

We have evidently to search among the materials that leave the body for substances that are, so to speak, chemical fragments of what was once living matter. In the expired air we have learnt to find the carbon dioxide and part of the water vapour that are products of the combustion of energy-yielding fuel. The fæces that are voided from the intestine are composed in the main of the undigested and indigestible residues of food and of the bodies of the countless swarms of bacteria that make up the individual's personal internal flora —in other words, materials that have never entered the tissues of the body at all. It is in the urine that we find concentrated the products that have been obtained by the breakdown of the living stuff. The urine has long been known to contain very considerable quantities of compounds rich in nitrogen, and it is among these compounds that we must search for the nitrogen that once formed an essential constituent of the protein framework of the tissues.

Chief among these nitrogenous compounds in the urine there is a substance which, from its occurrence there is called *urea*. This is a white crystalline substance readily soluble in water, and quite neutral (i. e. neither acid nor alkaline) in its properties. On the whole it is a rather indifferent substance and one whose properties adapt it for rapid and easy re-

moval from the body. Its chemical constitution is relatively simple, but as we have promised not to use any chemical formulæ we will not go into the details of that. It will be enough for our present purposes to mention that in addition to almost half of its weight of nitrogen it contains carbon, hydrogen and oxygen. It is quite easy by suitable methods to separate urea from the urine as it occurs there in such large quantities. A normal individual on an average diet produces rather more than an ounce of it every day. Now as soon as chemists had devised accurate methods for determining the exact amount of urea a man excretes in the urine per day, it was discovered that this amount is not the same under all conditions. One of the chief factors that influence the daily output of urea is the amount of protein eaten. When the amount of protein is increased so also is the output of urea in the urine; when the protein intake is diminished the urea production also falls. It is evident therefore that urea represents the end product—or at any rate one of the chief end products—of the complicated series of chemical changes that proteins undergo in the body. The amount of urea produced per day is thus a measure of the amount of protein that has been broken down during that time.

Now arises the important and interesting question, What happens when the man gets no protein at all—when, for example, he eats only bread and butter but no meat or similar nitrogenous food? It is then found that even on such a protein-free diet the output of urea does not cease altogether and, although smaller than that obtained on a normal diet, it is still considerable. As none of it can have come from the food (which we said contains no nitrogen) it follows that this urea produced during *protein starvation* must have come from the proteins of the man's tissues—that is, from his own living stuff. It represents a loss from his own essential self. As a result of the protein starvation he possesses less living

tissue than he did before—he is not the man he was. We have thus arrived at a method for obtaining some sort of measure of the rate at which a man's tissues are breaking down, of the rate, that is, at which his own personal proteins are being decomposed in his body in such a way that their valuable nitrogen is being converted into urea and so lost. When this sort of thing is happening the man is losing more nitrogen per day than he is taking in; he has, as we say, a negative *nitrogen balance*. Such a state of affairs obviously cannot continue indefinitely, for ultimately so much of the individual's proteins would be lost that there would not be enough of him left to remain alive. A normal person must receive in his diet as much nitrogen as he loses per day so that he is in a condition of what is called *nitrogenous equilibrium;* he is then receiving enough nitrogen to replace all that his tissues lose, and the total amount of living matter in his body remains constant.

In these considerations we have now encountered another very important question with respect to diet, for it becomes evident that we must give a man not merely sufficient food to supply the energy he needs for his daily life; we must at the same time see that that food includes enough protein to replace all that his body must inevitably lose by virtue of the mere fact that it is alive. But how much protein does this mean per day? How much of such things as meat and fish and eggs should our supposedly normal man eat? The way in which we obtain an answer to this question is very easy to understand: the reader could probably suggest it himself. It is necessary to give the man enough of carbohydrates and fats to supply him all the energy he is expending (thus making it unnecessary for him to use protein as fuel) and then to increase step by step the amount of protein nitrogen in his food until a diet is reached in which the amount of nitrogen he receives per day and the amount he gets rid of per

day are just equal. Under these conditions the amount of nitrogen entering the body exactly makes up for that which leaves it, so that the total amount of nitrogen in the body remains constant, i. e. no wastage is occurring. The body is then in the desired condition of nitrogenous equilibrium.

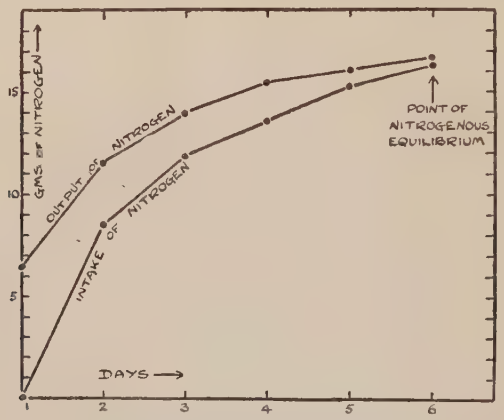


FIGURE 4. Curves showing the gradual attainment of the condition of nitrogenous equilibrium on increasing the amount of protein in the food of a dog.

(Courtesy of Messrs. Heffer and Sons.)

A great deal of important information as to the utilisation of nitrogen by the human body is obtained during the carrying out of such an experiment. As we have said, when nitrogen is completely absent from the diet the body still puts out a certain amount of urea and other nitrogen-containing substances derived from the breakdown of the tissues. When now we give our subject a small amount of protein in his daily rations the amount of nitrogen excreted is also increased, but not to the same extent as we have increased his nitrogen intake, so that on the whole his body is not so far from nitrogenous equilibrium as it was before. A further increase of protein in the food leads to a further increase

in the nitrogen output, but the proportion of nitrogen retained is still further increased with each increase in the amount of protein eaten until finally the amounts of nitrogen taken in and given out are equal and the condition of nitrogenous equilibrium is attained. The results of an actual experiment of this kind are depicted in figure 4 in which the curves for nitrogen intake and nitrogen output are both seen to rise as the protein content of the food is increased on successive days, but the latter more slowly than the former so that they ultimately come to cross at the nitrogen equilibrium point.

It might have been thought that all that would be necessary in order to achieve this condition of nitrogenous equilibrium would be to find out how much nitrogen the man gets rid of when he is receiving no nitrogen at all, and then to add this amount of nitrogen in the form of protein to his diet; but the actual curves show that in order to produce nitrogenous equilibrium it is necessary to give the man much more nitrogen in his food than he excretes during a period of nitrogen starvation. This means—and it should not be altogether a matter for surprise—that of any given amount of protein nitrogen that we consume only a certain fraction can be utilised by the body and the rest must be got rid of and so wasted. The nitrogen of proteins is, as we saw in Chapter II in the form of amino-acids, and the particular amino-acids occur in different proportions in the various proteins. Now in general it will be merely a lucky coincidence if the particular protein we give in the food contains the particular amino-acids in the same proportions as those in which the body is needing them: in general it will not be so. The food proteins will usually contain considerable quantities of amino-acids that the body does not want, and as, further, the body has but a limited power of converting one amino-acid into another, it follows that usually a considerable part of the nitrogen of the food must be

useless for the repair of the wear and tear of the tissues and so must inevitably be wasted.

But we have so far devoted all our attention to the principles of this question without any reference to the actual results of the practical experiment. What, you ask, is the amount of protein that must be eaten daily by a normal individual in order that he shall remain in nitrogenous equilibrium? Many experiments have been carried out along the lines we have indicated in order to obtain an answer to this question, and as time has gone on the estimate of the minimum quantity of protein required has been fixed at a lower and lower value. One of the most recent of such experiments, but at the same time a classical example, was carried out by Hindhede here in Copenhagen, where I am at the moment writing these chapters. He selected a vigorous healthy laboratory servant and kept him for a period of three months on a diet composed only of potatoes and margarine! Such a diet of course contains only a small proportion of protein derived from its vegetable constituent, and that protein not of the most appropriate for human nutrition, since there is a considerable difference in structure between potato protein and human protein: nevertheless it served to keep the man in nitrogenous equilibrium. For he was a very energetic laboratory servant, and carried out each day a very large amount of muscular work, not only during the performance of his official duties but also, after work hours, in the cultivation of his garden—an occupation for leisure hours that is much esteemed in Denmark. As a consequence of this he had to eat a very large amount of his monotonous diet in order to obtain enough carbohydrate and fat for use as fuel, and in so doing ate enough of the potato protein to supply his nitrogen needs. And when they came to analyse the food and to determine the actual amount of protein that he was receiving per day it was found to be only about 30 grams—

that is, not much more than an ounce a day. But in spite of this meagre diet he seems not to have suffered by the experiment, for medical examination at the end of the period showed that he was, as at the beginning, in normal sound health.

Now when we come to compare our ordinary diet with that of this poor unfortunate, we at once notice that it not only is much more varied but also, owing to our consumption of meat, eggs, fish and such products, contains a larger amount of protein—up to about four times as much per day. From the results of Hindhede's experiment we must say that so large an allowance of protein is certainly not absolutely necessary; we take it mainly because it suits our palate —the protein foods being usually more tasty than starches or fats. What then becomes of the excess of nitrogen that we thus obtain? The answer is that it is just wasted. It is split off from the protein during the chemical changes to which these are submitted in the tissues, and ultimately appears in the urine—mainly in the form of urea. The residue of the excess proteins—their carbon and hydrogen—are used ultimately, if not immediately, as part of the fuel supply of the body, and, like similar constituents obtained from other food-stuffs, can be stored in the form of animal starch (see page 40) until required. But the body seems to have very little power of storing any excess of nitrogen that may be eaten. We carry large reserves of such fuel substances as fats and carbohydrates, but seem to have no provision for the carrying of any spare proteins. Expressing it in scientific language we should say that if an individual is in nitrogenous equilibrium on a diet containing a certain amount of protein per day, then he will be in nitrogenous equilibrium on all diets containing a larger amount of protein. It would seem, therefore, that there is no reason for consuming an amount of protein larger than the minimum required to

maintain this condition of nitrogenous equilibrium—from the point of view, that is, of the maintenance of the tissues. It may be nice to take a larger amount, indeed it might be said that it is the extras that make life worth living. But physiologically necessary it appears not to be.

This conclusion has a very important bearing in another connection. For, as it happens, it is the protein constituents of our diet that are the most expensive: it is just these constituents therefore that are likely to be insufficiently represented in the diet of the poorer classes. It is consequently very important to know whether the diet of the poorer classes of a community is such as to render possible the maintenance of nitrogenous equilibrium in its individual members, for if it is not, then their bodies are wasting—the amount of living matter in them is diminishing—and the society of which they form the foundation is heading for collapse. When a nation as a whole gets out of nitrogenous equilibrium it soon gets out of political equilibrium as well.

When we were speaking of the total combustion occurring in the body we pointed out that the various members of a community require diets yielding very different amounts of energy for the performance of their various tasks, the actual number of calories necessary in any case being determined by the amount of physical labour that the daily duties demand. But with regard to nitrogen requirements the case is different. The amount of wear and tear going on in the body as a whole is practically the same, other things being equal, whether a large or a small amount of muscular work is being performed. It will naturally vary somewhat according to the muscular development of the individual, for in the powerful muscles of a blacksmith, for example, there is more living matter to maintain than in the puny muscles of a sedentary indoor worker, but on the other hand the indoor worker usually demands a relatively high proportion

of appetising protein food as he has not the opportunity of developing the same healthy appetite for plain food as his more active fellow, so that the difference in the protein content of their diets comes to be not so great after all.

In the early days of the study of biochemistry—before there existed really accurate methods for the determination of the total amount of nitrogen entering and leaving the body, and in particular for the analysis of urine—it used to be thought that the energy for all muscular movement was obtained by the decomposition of proteins, and that the combustion of carbohydrates and fats served merely to maintain the warmth of the body. This old view—which, it will be noticed, is just the opposite of what we believe to-day—was based on the idea that the more work a man did the greater the output of nitrogen in his urine and the greater therefore his need of this constituent in his diet. But as soon as more accurate methods of investigation were brought to bear on the problem this view had to be given up. One of the most interesting of the experiments that led to our modern view that carbohydrates and fats are used as fuel for the production of mechanical energy in the muscles, was carried out by two German physiologists, Fick and Wislecenus, about forty years ago. They decided to perform a known amount of muscular work by climbing a mountain, and for the purpose they selected the Faulhorn in Switzerland. The height through which they climbed was known, also the weights of their bodies, so that the actual amount of mechanical energy that each climber expended was known. They analysed the urine produced during the climb and thus found the amount of protein that had been broken down in their bodies during the work. Allowing for the amount of protein they would in any case have decomposed if they had not undertaken the climb (this they determined by analysing the urine formed during the resting hours be-

fore they set out) they found that the extra amount of protein used during the expedition was far too small to yield the energy required for hauling their bodies up to the top of the mountain. They must therefore have used a considerable amount of non-nitrogenous fuels—carbohydrates and fats —for the purpose.

The proteins are used therefore primarily for the purpose of maintaining the tissues and replacing such material as is slowly being lost from them. Only when more protein is eaten than is required for maintenance, or when such protein is eaten as is not suitable for this purpose, is it used as mere fuel. In the case of a growing organism, however, the protein has a further important use of providing material for the new living matter that is being produced. We have already said that it is only the fully grown organism that can ever be in a state of nitrogenous equilibrium. A growing child, therefore, will require *relatively* more protein, that is, more protein per pound of body weight, than will a fully grown adult. So much so that under ordinary circumstances it is practically impossible to get a child to eat too much protein.

Another type of individual who cannot be in nitrogenous equilibrium is the person who is convalescing from an illness involving fever. During the fever the tissues of the body break down at an abnormally fast rate so that by the time the patient has overcome the bacteria or other organisms which are causing the fever his body is very considerably wasted. During the convalescence, therefore, he will require a diet rich in protein in order that what has been lost may be replaced.

Evidently those food proteins are most adapted for the maintenance of the tissues that can supply the various amino-acids in the proportions in which the body is losing them. On the whole, vegetable proteins differ very considerably from

animal proteins in the proportions in which they contain these amino-acid constituents, and some vegetable proteins are known from which certain important and necessary amino-acids are lacking altogether. So that, to say the least, the man who eats only vegetable proteins (and not many do, even vegetarians usually supplementing their diet with some animal products such as milk and eggs, so that we should say, rather, a man who did restrict himself entirely to vegetable foods) would have to eat considerably more of them in order to get a sufficiency of nitrogen that is combined in the needful forms. The nearest approach to the ideal protein would seem to be the protein that the body itself is losing, that is, the protein of human tissues. Perhaps this is the physiological basis for the superstition current among cannibal tribes that if you eat your enemy's heart you acquire his bravery and strength. For more civilised folk there is another means of achieving the same end, and that is to use a well assorted mixture of proteins in one's diet. In this way an amino-acid that happens to be lacking from one protein can be supplied from another protein in which it occurs in abundance, so that by a judicious choice of proteins all the needed amino-acids may be provided.

This possibility is very well illustrated by the proteins of milk. Of these, casein is completely devoid of the sulphur-containing amino-acid *cystine,* and since human tissues contain this amino-acid no amount of casein by itself could serve to build up new human proteins. Its "biological value," as it is said, is zero. But *lactalbumin,* the other protein of milk, contains an abundance of cystine, so that the naturally occurring mixture of these two proteins will supply all the amino-acids that the body requires: in other words, the mixture of these two proteins has a very high biological value. In the same kind of way gelatine is lacking in some of the most essential of the amino-acids so that by itself it is quite

unsuited for rebuilding the wasted tissues of a convalescent. Its biological value is therefore also zero; but used in conjunction with other proteins it may serve as a valuable source of such amino-acids as these additional proteins may not contain.

For the sake of any who are anxious to pursue this subject further we ought to explain that if we knew a protein in which the mixture of amino-acids was just such as is required for the production and maintenance of human tissues we should take the biological value of this protein as 100. The biological value of any other less complete protein would then be measured by the number of ounces of human tissue to which 100 ounces of such a protein could give rise. From the examples we have just given it will be seen that the absence of a single amino-acid is sufficient to reduce the biological value of a protein to zero, but that the biological values of *mixtures* of proteins are usually high—a splendid argument in favour of taking a "good mixed diet." In order to help the reader to do this we quote from Professor V. H. Mottram the following list of amounts of various protein-containing food-stuffs that must be eaten in order to give the body 30 grams of protein of high biological value.

AMOUNTS OF VARIOUS FOODS CONTAINING 30 GRAMS OF HIGH-VALUE PROTEIN

4¼ oz. cheese
5½ oz. lean beef
7 oz. lamb
7½ oz. mutton
7½ oz. ham (lean)
8 oz. pork
4–4½ (i. e. 9 oz.) eggs
10 oz. cod
11 oz. mackerel
12 oz. fat bacon
2 pints of milk.

If a man takes any one of these rations per day (or half of one and half of another, and so on, according to his taste)

it is certain that, with the help of the less valuable proteins contained in his vegetable food, his protein requirements will be covered. It is of course to be understood that this protein ration forms part of, and is *not* additional to, the energy ration about which we said so much in the preceding chapter.

It will have been noticed that throughout the present chapter we have considered the nitrogen loss from the body as being practically all in the form of urea. But we ought to add that there are a number of other nitrogen-containing substances that occur in the urine. They are produced in very much smaller quantities than urea, but their properties and relationships are none the less interesting on that account. Of these substances we will mention only one called *uric acid,* which must be already well known by name, at least, to everyone who reads (and who does not?) the patent medicine advertisements that add a sprinkling of realism to the romantic pages of our modern magazines. This uric acid is a white crystalline substance that forms a marked contrast to urea inasmuch as it is only very sparingly soluble in water. For this reason it has the unpleasant habit of separating out in the form of sharp, pointed crystals before it has been transported from the tissues and got rid of from the body, and in this way is responsible for the discomfort of gout and similar disorders. Thus, although it contributes only a small fraction of the total nitrogen output of the body, uric acid is of very great importance from the medical point of view.

Again, urea itself has a further interest apart from the fact that it contains the bulk of the nitrogen got rid of from the body. For urea was the first substance associated with life processes to be prepared "artificially" in the laboratory. Just over a hundred years ago the German chemist Wöhler discovered that by surprisingly simple means he could manufacture urea from non-living materials. Up to that time the only source of it was the urine of living ani-

mals. To us in these days there seems nothing very unusual about such a discovery, for we are accustomed to hearing about the synthesis by chemists of useful materials first found in the bodies of animals or plants. Everyone knows synthetic indigo as a striking example. But a century ago this discovery of Wöhler's evoked a considerable amount of surprise and even of ridicule. Even so great a chemist as Liebig refused at first to accept it. For up to that time the investigation of the chemical processes occurring in the body had proved to be so difficult and puzzling that everybody had become firmly convinced that the changes associated with living matter were much too mysterious ever to be imitated in the laboratory. It was thought that the products elaborated by living organisms were formed only under the action of some special "vital force" whose workings would ever remain incomprehensible. But with one brilliant stroke Wöhler swept these vague nebulous ideas aside by showing that a product so characteristically biological as urea could be made in the absence of living matter and from quite ordinary and familiar materials taken from his laboratory shelves.

Since Wöhler's day innumerable other products and constituents of living organisms have been built up from their elements, and the work is still going on. Certainly there still remain many many substances whose chemical constitution we do not know and for the supply of which we are still dependent on living organisms. But this seems to be merely because we have not yet devised the methods of investigation appropriate to these particular cases. That the changes going forward in living organisms are so complicated as to require very special methods of investigation we cannot deny; but that they differ in essential nature from the simpler changes that occur in systems where life is not concerned we see no reason for believing.

IX

DIGESTION AND INDIGESTION

THE close of the last chapter brought us to the end of one of the chief sections of our subject. Up to the present we have considered the body as a whole from the point of view of its needs for energy-producing fuel and for material for the maintenance of its structure. In order to obtain information on these points we had to study the composition of the food the body takes in and the nature and amount of such waste products as carbon dioxide, water and urea that it gives out, but we did so without inquiring into the details of the long series of chemical changes of which these last-named substances are merely the end products. From the point of view of the body as a whole this treatment was quite sufficient, but it is evident that our knowledge must always remain incomplete without some information as to the complicated chain of chemical reactions that produce and maintain an active creature from the starches, sugars and proteins with which he is supplied. At the present time biochemists in laboratories all over the world are concentrating their energies on the unravelling of this intricate tangle of interwoven reactions; in so doing they are attempting to solve some of the most supremely difficult problems with which the human mind can grapple, so that it is not surprising if we have to confess that at the moment they have hardly done more than identify a few of the threads.

It would therefore be quite out of place in a book dealing only with the barest outlines of the subject to attempt to give any detailed account of the information to which all these efforts have led us. All we can hope to do is to choose out certain aspects of the subject where there exists enough knowledge out of which to weave a continuous story, and to relate this in the hope that it may prove not merely interesting but also stimulating to further study.

One such aspect of our subject is that which concerns the processes of digestion, the processes, that is, to which the food is subjected before it is actually presented to the tissues for their use. Our knowledge of these processes, although by no means complete, is certainly fairly extensive, because we can fairly readily obtain specimens of the digestive juices, and can study their action outside the body in flasks and test-tubes. This is much easier than studying those chemical changes that go on only in the living tissues themselves. In fact the processes of digestion are among the easiest of the chemical reactions of the body to investigate, and yet the results obtained by their investigation have such a general importance with regard to the other processes occurring in living matter that they well deserve our attention. Apart from this the process of digestion has a very personal interest for each of us, for we are more at the mercy of our digestive apparatus than we are at that of our cooks. If a particular food or dish is not to our taste we can reject it, and as long as our energy and protein requirements are made up somehow else our health will not suffer. But once we have swallowed the food, if our digestive apparatus fails to prepare it suitably for the use of our tissues then, in spite of an appropriate intake of food we may remain undernourished and our philosophy of life may be considerably affected as a consequence. Affected—yes; but perhaps not invariably for the worse, if we are to believe those unkind critics

who have ascribed some of the world's masterpieces of literature to the disturbed digestions of their authors. But then perhaps to be an author at all one must always be a little ill. . . . It may be so, but in any case we cannot here go into the question as to what kinds of chemical reactions, occurring in the body, are most likely to lead to the production of artistic masterpieces. All we can hope to do is to describe some of the initial stages in the utilisation of food that occur in all of us whether our productions are masterpieces or no.

When we eat food we take it into a long tube made up of the œsophagus or gullet, the stomach, and the intestines. This tube, seeing that it is so intimately concerned with the nourishment of the body, is called the *alimentary canal*. In it the various constituents of our foods undergo the first of those far-reaching chemical changes that must take place before they can be used for the production and maintenance of the constituents of human tissues. It has long been known that these initial changes in the food are brought about by the action of a number of digestive juices that are poured into the alimentary canal and are mixed with the food by the activity of the muscles of which the wall of the canal is largely composed.

The *saliva* which is poured into the mouth when we eat—or when, as we say, our mouths "water" at the thought of appetising food—and which is mixed with the food during the muscular activity of chewing, is the first of these digestive juices, and as it is so accessible for observation—everyone having his own little plant for its manufacture—we will consider it in some detail. Perhaps at the outset we ought to say a word about this little manufacturing plant that we have just mentioned, although this is a topic that belongs more strictly to the realm of physiology than to that of biochemistry, so it does not concern us a great deal. The saliva is made

in a number of what are called *glands*. The Latin *glans, glandis,* means an acorn or nut, and the organs we are about to describe are so called because when the older anatomists discovered them they did not know what was the function of these organs, and so gave them a name which merely called attention to their size. Perhaps they thought that all organs of about the same size had the same kind of function. There are many glands in the body and many of them are very different in size from acorns but they all have this in common: that the function of each is to manufacture some product or products that the body requires. The glands that produce the saliva are altogether six in number—three on each side—embedded among the muscles around the mouth, and they send the saliva they produce into the mouth through small tubes or ducts.

When we come to examine the structure of one of these salivary glands under the microscope, we find that it contains a large number of little hollow cavities whose walls are composed of more or less brick-shaped living cells. These cavities communicate with branches of the duct, and the cells that form their walls are the cells that actually manufacture the saliva and "secrete" or push it into the duct and so out into the mouth. The whole arrangement is something like a bunch of grapes in which the separate grapes represent the individual little cavities of the gland and their stalks represent the little ductiles which, uniting with others similar to themselves, lead finally to the main trunk of the bunch, which represents the main duct of the gland. We should mention that not all glands are as complicated as this: the essential feature is always a layer of secreting cells that manufacture the gland products, but the exact arrangement of these cells is different in different glands. In the simplest cases of all they may form a single layer on a simple flat surface; or they may cover a surface that is folded or wrinkled

or pitted so that they line the sides of the pits; or we may have the very complicated type of folding we have found in the salivary glands and that renders possible the packing of a very large number of active cells into a comparatively small and compact organ.

But what concerns us most at the moment is not so much the detailed structure of the salivary glands as the composition and functions of the saliva that they produce. Everybody who gives it a moment's thought will at once realise that one important use of the saliva is the purely mechanical one of acting as a lubricant for the food masses that are being swallowed. The saliva owes its lubricating action to the presence in it of very considerable quantities of a special protein called *mucin,* which forms a very slimy solution when dissolved in water, and which is produced in many parts of the body where lubrication is required. Mucin is in fact the natural lubricant of the body. But while this lubricating action is such an obvious one to everybody, we rarely have an opportunity of realising what an essential part it plays in the mastication and swallowing of food. Perhaps it will not be out of place if I illustrate this point by mentioning an instance that came to my own personal notice. On one occasion a student of mine came to me for instruction and happened to mention that he was very hungry. Thinking for the moment that this was because he, as students will, had happened to spend too large a part of his income on pleasures more attractive than mere food, I at once offered him a meal, but he went on to explain that this would be quite useless as he was unable to eat. On further inquiry I found that for quite another purpose his physician had ordered him a medicine containing the drug atropine, and that by mistake my student had taken a double dose of it that morning. As it happens, atropine has the property of numbing or paralysing the nerves that control the functioning of the salivary glands

(among other organs); the result was that the nerves could not stimulate the glands to secrete saliva when this was required, and as a further result my student found that in the absence of saliva it was impossible to swallow any solid food. Of course this condition lasted only a day or so and passed off as soon as the atropine had been eliminated from his body, but while it lasted it furnished very striking evidence of the assistance the saliva gives us in the swallowing of our food.

But even so this lubricating action cannot be said to be the most important function of the saliva. It has a very powerful digestive action as well: that is, it begins the breakdown of the raw materials we take in as food into products that the body can utilise for the energy-yielding and tissue-repairing functions we have discussed at such length in previous chapters. To go straight to the root of the matter, we will say at once that the particular food material on which the saliva acts is *starch*. Starch, if it found its way into the tissues of the body, would be quite useless to them. Apart from its harmful effects in blocking up small blood vessels and similar structures it would be a quite indifferent substance. But if it is first acted upon by digestive juices there are obtained from it substances that the tissues can burn and utilise. As this action of saliva on starch is interesting and important, both for its own sake and also because it illustrates very beautifully some general points concerning the way in which chemical changes are brought about, not only in the digestive processes of the alimentary canal but also in the body as a whole, and as furthermore this action is one which anyone can observe for himself, we shall describe it in some detail so that the reader can use our description as a guide in performing the experiment with his own hands. If only he will do this we can assure him that he will get a much

better grasp not only of the subject matter of this present chapter but also of the whole of this book.

First, we want a solution of starch. This is easily obtained by taking a pinch of ordinary household starch, rubbing it up into a thin paste with a drop of water and then pouring on to it a few spoonsful of boiling water, stirring the while. Let it cool before use. Next, the saliva. This is most conveniently collected by holding in the mouth a quantity of warm water until it is felt that a considerable amount of saliva has been secreted into it, and then ejecting this into a suitable glass. Lastly, we must have some means of telling whether the starch is remaining in our mixtures or is being digested away into other products. In order to do this we take advantage of the fact that starch gives a very characteristic dark blue colour with iodine. A convenient way of obtaining a suitable iodine solution is to dilute with water the ordinary tincture of iodine that the druggist supplies for dressing small wounds, until its colour is a light yellow. A drop of this solution will give a deep navy-blue colour with any solution containing starch. Try it with a drop of the starch solution you have just prepared, but do not add the iodine to the whole bulk of the starch solution or you will render it useless for the experiment. Take a drop of the starch solution on a white plate, bring a drop of the iodine solution near it and then, when all is ready, just mix the two drops and observe the effect.

Now to see the digestion of the starch by the saliva. Take some of the saliva in a test-tube or, failing this, a little bottle—a couple of tablespoonsful is all you require: add two or three drops of the starch for the saliva to act on. If now you take out a drop of this mixture and mix it on the plate with a drop of iodine, you will of course see the blue colour produced by the starch; but if you keep the mixture of starch and

saliva warm (dip the little bottle or tube into water no hotter than your hand can easily bear, or tuck it up snugly inside your clothes somewhere) you will find that after a few minutes, or even seconds if the saliva is strong and you have not added too much starch, a drop of the mixture will no longer give a blue colour with a drop of the iodine. The starch has been digested away and changed into other products.

It would not be particularly easy for the reader who has no laboratory at his command to determine what these breakdown products are, so we shall have to tell him. When starch is acted upon by saliva, sugar is formed, and the particular sugar that we obtain in this way is malt sugar. We have already spoken of this sugar in Chapter III—indeed we there mentioned it as being obtained when starch is broken down. In the same place we also said that the production of this malt sugar from starch is not just a simple chemical change, but passes through a number of stages at which intermediate products are first formed, which are in turn decomposed further into the sugar. The reader will remember that we mentioned the dextrins in this connection. Now it is quite easy for him to show that dextrins are produced on the way, so to speak, between starch and malt sugar. All he has to do is to perform the salivary digestion experiment we have so fully described, and to test a drop of the digestion mixture with a drop of iodine on the white plate every few seconds as the digestion proceeds. He will then find that soon after the beginning of the digestion the mixture gives not the blue colour characteristic of unchanged starch but a brownish-red colour. This red colour is produced by the action of the iodine on the dextrins that are first formed from the starch. Then as the process continues the power of giving this red colour is also lost and the "colourless" point is reached at which all the starch and

the dextrins have been decomposed and there remains only sugar in the solution.

Now we said also in Chapter III that just such a breaking down of starch can be brought about by boiling it with a little strong acid. But now we find that the saliva contains some agent that is capable of bringing about this same change without requiring the solution to be heated above the ordinary temperature of the body and without the addition of a strong acid. Of course we ask at once: What is this powerful agent the saliva contains? and what is the mechanism by which it can bring about in slightly warm, practically neutral, solution chemical changes for which we require in the laboratory high temperatures and strong reagents? It is the case with these, as with so many of the questions that confront us during the study of biochemistry, that our knowledge at the present day is not sufficient to enable us to answer them completely; nevertheless we do know a great deal about this and the host of similar agents that living organisms produce and use for bringing about chemical reactions that are necessary for their life processes, and it is quite easy for the reader to acquaint himself with some very important and fundamental aspects of this knowledge at first hand from a study of the materials themselves.

Let him, for example, perform the experiment to illustrate the digestion of starch by saliva, and when he has arrived at the stage at which the iodine test shows that no more starch remains in the digestion mixture, let him add a further quantity of starch solution, and, keeping the mixture warm, let him follow the course of subsequent events, using drops of iodine on the white plate as before. He will now find that this second portion of starch is digested as readily as was the first, and when his solution is again starch-free he will find that yet a third and other further quantities of starch can still be acted upon by the same original quan-

tity of saliva with which he started. This will be enough to convince him that the active substance of the saliva, while bringing about this digestive action is not used up during the process; it can be used over and over again and at the end still remains as capable of breaking down a further quantity of starch as it was at the beginning.

Now the chemists who study non-living matter know a great number of substances which, when present in small quantities, can bring about chemical changes in very large amounts of other materials without themselves being apparently changed during the process. Such substances which seem to act by their mere presence the chemists call *catalysts,* which means "breakers down," and here in the saliva we have evidently a substance of the same class, but one that has been produced in the body—we have, in other words, a *biological catalyst.* This particular biological catalyst present in the saliva is called *ptyalin,* from the Greek πτυο, I spit. Now an important characteristic of this ptyalin (and for that matter of biological catalysts in general) is its sensitiveness to heat. It is destroyed if heated to boiling. This again the reader can easily see for himself by collecting some more saliva, dividing it into two portions and heating one to boiling. If now he will try the starch digestion experiment with the two portions of saliva, he will find that the starch will remain unchanged in the boiled portion and will give its characteristic reaction with iodine when that in the unboiled portion has long since disappeared. Biochemists have studied the influence of many other factors besides heat on the activity of ptyalin: they have found that some of these factors favour its action while others exert a hindering or inhibitory effect on it. In this way a great deal of information has been obtained as to the conditions of its action, but up till now we have no method of separating it in a pure condition from saliva, so that we cannot say exactly

what it is or exactly how it acts. It is certain, however, that it is a complicated substance, and most probably it is a special kind of protein.

We have dealt thus at such great length with ptyalin because, as we have already hinted, it is but one example of a whole host of similar biological catalysts that are produced in living organisms for the purpose of bringing about chemical changes which those organisms require for their life processes. By studying the activities of the digestive action of saliva on starch the reader has made himself familiar with the general way in which chemical changes in all living matter are brought about. We need make no excuse, therefore, for the detailed attention which we have given to it. It must not be imagined that all these biological catalysts act on starch; some act on proteins, some on fats, some on other materials, and it is found that each particular catalyst will act only on one particular substance or group of substances. Its tastes are usually very restricted and it will deal only with those substances for which it is, so to speak, specifically adapted, so that it will be readily understood how it is that we require a separate catalyst for each individual reaction that has to be brought about.

But let us emphasise the point that it is not only digestive processes that depend on the activities of these catalysts. All the complicated chemical changes that occur during the utilisation of digested food for fuel and for maintenance are also brought about with their aid, and not only in ourselves but in all other living things, both animals and plants. Indeed, the very first of these biological catalysts to be recognised was the one that occurs in the lowly but useful little plant, *yeast,* to which we might refer before we proceed with our further account of the processes of digestion in ourselves. A lump of ordinary yeast is composed of an enormous number of tiny yeast cells. It has been known

from time immemorial that when these get into a sugary fluid, such for example as fruit juice, they cause the sugar to be broken down into alcohol and carbon dioxide. The alcohol gradually accumulates in the fluid and can be put to appropriate use; the gaseous carbon dioxide bubbles off and in so doing gives the liquid the appearance of boiling or "fermenting" (Latin *fervere,* "to boil"). It is from the energy liberated in this reaction that the yeast plant obtains the energy required for its life and growth. Now it used to be thought that this breaking down of sugar could take place only inside the living matter of the yeast cell, until in 1897 the German chemist Buchner showed that in order to convert sugar into alcohol and carbon dioxide it was not at all necessary to have the living yeast cells present in the fluid, that the juice that can be squeezed out of the yeast will do just as well. In other words, it is not necessary to have living matter present if we have a supply of the biological catalyst that it produces. Buchner realised that this biological catalyst that he had thus isolated from yeast was but one example of the great class of biological catalysts which bring about chemical changes in living matter in general, and he invented the name *enzymes* for these important chemical agents, taking the word from the Greek εν ζυμη, meaning "in yeast," as a reminder of the organism from which he had obtained the first member of the group to be recognised. From now on we shall follow his example and shall use the word enzyme to mean a biological catalyst: many authors use the older word *ferment* with the same meaning, indicating that the first biological catalyst whose action was observed in the absence of living matter was that associated with fermentation.

Here then we have made acquaintance with two members of the fundamentally important group of enzymes or ferments—the ptyalin of the saliva and the ferment of yeast.

Each of these illustrates the characteristic properties of the group, for the yeast enzyme, like ptyalin, can exert its activity on only the particular substance to which it is adapted (in this case sugar) but of this it can deal with a practically unlimited quantity, and like ptyalin also it is very sensitive to the influence of temperature and other circumstances.

From all we have said so far the reader will not be surprised to learn that from the point of view of the biochemist the study of digestion consists mainly in an examination of the various juices formed in various parts of the alimentary canal and a study of the activities of the enzymes that these juices contain. We have already studied fully the enzyme of the saliva. We must now go on to consider those of the other digestive juices.

When the food mass has been swallowed down the gullet or œsophagus into the stomach, it there meets the second of the important digestive juices that act upon it. This "stomach" or *gastric juice* is formed in a large number of little glands situated in the inside lining of the stomach; these do not send their prepared juice into one main duct, as is the case with the saliva, but pour it out separately over the whole inside surface of the stomach each through its own tiny pore. In this way it comes thoroughly into contact with all parts of the food, the mixing process being helped by the movements of the muscles of which the outermost part of the stomach wall is made. The gastric juice is not so readily accessible for experiment as the saliva, but in spite of this its action was studied by many of the older physiologists. The old abbot Spallanzani, for example, who from his own observations seems to have known as much about physiology as anyone during the latter half of the eighteenth century, devised the ingenious plan of collecting gastric juice from animals by causing them to swallow sponges on strings. When the sponge was judged to have

soaked up a sufficient quantity of the gastric contents, it was pulled up again and the contained fluid squeezed out and examined. Nowadays the examination of stomach contents is often resorted to as an aid in the locating of disturbances of digestion, and although the method used is the same in principle as that employed by old Spallanzani, it is carried out in a somewhat more refined manner. The patient has to swallow a long narrow tube of india rubber carrying a suitable nozzle which keeps the end of the tube open when it is down in the stomach. The end that projects from the mouth is connected to a suitable pump and collecting apparatus by means of which the gastric juice can be sucked up and collected for examination.

It was not long before it was discovered that the fluid collected by such methods as these has a very powerful action on protein materials. It is quite easy to follow the way in which, if it is kept warmed up to body temperature, it will dissolve completely little pieces of meat or boiled white of egg. If the fluid be previously boiled, on the other hand, it will be found to have lost this action entirely. Evidently, therefore, we are here dealing with another enzyme similar in its general properties to those we have already studied, exerting its action, not on starch or sugar, but on proteins. The name given to this stomach enzyme is *pepsin* from the Latin *pepsis,* meaning "digestion," for the stomach is that part of the whole alimentary canal which is most obviously associated with digestion.

This enzyme pepsin is not the only important constituent of the gastric juice. Everybody knows that, when as a result of some internal irritation vomiting has been caused, the gastric contents have tasted markedly acid. And as a matter of fact the gastric juice is always quite acid; it contains an appreciable amount of *hydrochloric acid.* This acid is obtained ultimately from the ordinary salt (sodium chloride)

that we eat, and it is a fact that if this acid is not present the action of pepsin on proteins is practically stopped. As a general rule we can say that each enzyme requires a particular kind of medium for the exhibition of its maximum activity. Ptyalin, we saw, acts in a liquid that is practically neutral, namely the saliva, and is in fact destroyed by acids; here, on the other hand, we find that pepsin will act only when a considerable quantity of acid is present.

If the reader after his experiences with the salivary enzyme feels inclined to try any more experiments he can easily demonstrate these properties of pepsin for himself. It is not at all necessary for him to get up any of his own gastric juice, for there are several commercial preparations of pepsin on the market. They are obtained by making extracts of the inner lining of the stomachs of cattle slaughtered for food. Such a preparation is put out, for example, by the Armour Company. In order to make a suitable solution it is necessary merely to take a little of Armour's preparation of pepsin and to dissolve it in about two hundred times its weight of water—that is, a teaspoonful to about a pint and a half of water. The necessary hydrochloric acid must be obtained from the druggist; the right strength is .4 per cent; this being the strong acid diluted with about 100 times its volume of water. As material to be digested we can take small shreds from the white of a boiled egg. In order first to show the digestive action, take some of the pepsin solution in a glass, add an equal quantity of the acid and then one or two flakes of the egg white. Remember carefully how much egg white there was at the beginning, and then place the mixture somewhere where it can be kept gently warm for half an hour. It is really most convenient to use glass test-tubes for these experiments and to keep them warm by standing them in a can of water that is just comfortably warm to the hand. Look at the digestion mix-

ture from time to time, and if only a few shreds of egg white were added at the beginning it will soon be very easy to see that they are getting smaller and slowly dissolving. To show that we are really dealing in this case with the action of an enzyme, that the pepsin is not used up during the digestion but remains in the fluid ready to act on further supplies of protein, it is necessary merely to add to the digestion mixture a few more flakes of egg white when the first ones have become completely dissolved; and still further additions will in their turn disappear if the mixture is kept warm. It is not uninteresting to go on and see how much egg white one particular portion of pepsin will digest.

That the pepsin is as sensitive to heat as we found ptyalin to be, is very easy to show. All that is necessary in this case is to boil some of the pepsin solution before adding the acid and egg white to it: it will then be found that the egg white remains unchanged in the fluid in spite of long-continued warming, showing that the pepsin has now been destroyed. Lastly, in order to show how important it is to have the acid present, just make up a mixture of the pepsin solution with an equal quantity of plain water and float some bits of egg white in this; keep this mixture warm as before and it will be found that the egg white remains quite unattacked. The same kind of method can be used for getting an estimate of the amount of pepsin there is in a sample of gastric juice. In this case the egg white is drawn up while raw into small glass tubes. It is then coagulated by placing the tubes in boiling water. If such a little egg white tube is now dropped into gastric juice, the egg white is gradually digested along the tube, beginning from the ends, where, of course, the egg white comes into contact with the solution; and the rate at which it is digested gives us a measure of the potency of the gastric juice we are testing.

So far we have not mentioned what the products are that

are formed from egg white and other proteins when they are dissolved and digested in this way by pepsin. When pepsin acts upon proteins it breaks them down partially, but not completely: the resulting products are still proteins, but proteins simpler in chemical structure than the food proteins from which they were derived. In Chapter II we explained how the complicated chemical structure of a protein is built up of amino-acids. Egg white and similar proteins are composed of enormous chemical complexes of these amino-acids and when pepsin acts on them these complexes are partly disintegrated and the resulting products, while still being composed of chemically linked groups of amino-acids, are relatively simpler as regards both the number and arrangement of these groups. Figuratively speaking we may say that under the influence of pepsin the long and complicated chain of amino-acids is not broken down into its individual links but that it is at all events split up into shorter and simpler lengths. Of these simpler proteins a number of kinds are known: they differ among themselves mainly in respect of their differing solubilities in various salt solutions. We will content ourselves by mentioning just one of the most important of these kinds, namely the group of the *peptones*—so called because they are formed from the more complicated proteins by the digestive action of pepsin.

We have now followed the digestion of the food to the stage where it is passed portion by portion from the stomach into the first part of the long coiled tube of the intestine. Some, if not all, of the starch will have been broken down into malt sugar by the ptyalin of the saliva, and the proteins will have been broken down into peptones by the pepsin of the gastric juice. But the food has to be submitted to the action of several more digestive enzymes before it is broken down into products that are suitable for presentation to the tissues. For one thing, we have said not a word about the di-

gestion of any fat that the food may contain—and most of us like a little butter to our bread.

Now tucked away among the first coils of the intestine there is a gland called the *pancreas*. It is what the butcher calls the sweetbread. In structure it is not at all unlike a salivary gland, and, like the saliva, the juice the pancreas produces is collected into one duct through which it passes into the intestine where it becomes mixed with the food. It is evidently much more of a task to collect pancreatic juice for experiments than it is to collect either saliva or gastric juice because in order to get at the pancreas or its duct something of an operation is required. As long ago as 1664, however, the old Dutch physiologist Regner de Graaf achieved the object by inserting into the duct of a dog's pancreas a quill long enough to reach through a cut in the abdominal wall to the outside of the animal. Nowadays a similar result is obtained by cutting out the little piece of the intestine into which the pancreatic duct opens and sewing it into the skin of the abdominal wall. One must be careful not to damage the connection of the duct with the pancreas itself, so that when the wound has healed up the pancreatic juice passes not into the intestine but to the outside of the body and can be collected in a bottle hung under the dog's belly. A dog that has been treated in this way can go on living a practically normal life, provided care be taken to give it a diet that it can digest without the use of the pancreatic juice, and it can therefore be made to give us a great deal of information concerning the composition of this juice and the conditions under which it is formed. This method of operation and experiment has therefore been much used in later work, particularly by the Russian physiologists, who under the leadership of Pavlov, have made a special study of the production and composition of the digestive juices. It is possible to collect from a human subject a sample of pancreatic

juice, or, more strictly speaking, a sample of the mixed contents of the first part of the intestine, by getting him to swallow a stomach tube of the kind we described, and waiting until the end of this has been carried right through the stomach into the beginning of the intestine itself. But generally when pancreatic juice is required for demonstrating its actions in the laboratory it is obtained by making a suitable extract of a pig's pancreas acquired from the slaughter house. There is also a pancreatic extract produced commercially under the name of *liquor pancreaticus*.

Before we go on to speak of the digestive actions brought about by the pancreatic juice obtained in these various ways there is one general point to notice about it, namely, that, unlike the gastric juice, it is not acid. On the contrary it is markedly alkaline. Furthermore the point at which the pancreatic duct enters the intestine is very close to the place where the bile duct enters and brings in the *bile* produced in the liver. And this bile is also very markedly alkaline on account of the large amount of soda it contains. This means to say that all the actions that the pancreatic juice brings about occur in this alkaline mixture.

Now when we come to examine the effect of pancreatic juice on a number of substances, we find that it contains a whole array of enzymes. Of these, one exerts a very powerful digestive action on fats. We will consider this first as we have not yet met an enzyme capable of acting on food materials of this kind. In our description of the fats in Chapter III we laid special emphasis on the circumstance that these substances are compounds of the fatty acids with glycerol (glycerin). We also saw how by boiling with strong caustic soda solution these compounds could be broken up and the fatty acids and glycerol set free. Now the fat-splitting enzyme of the pancreatic juice brings about exactly this same change, so that here we have yet another case where an en-

zyme can bring about under conditions that exist in the body a chemical change for which in the laboratory we must use strong agents and boiling temperatures. This fat-splitting enzyme, then, decomposes the fats of our food into glycerol and fatty acids and these latter, in the alkaline medium in which they find themselves, at once combine with some of the soda to form soaps. In this action the pancreatic juice is very much helped by the bile. For as the fats will not mix with water it is evident that the digestive juices cannot soak into them and act upon their whole mass as is possible in the case of starches and proteins. The fat can be acted upon by the digestive juice only on the surface of each separate lump. But the bile contains some special salts that have the useful property of causing the fat particles to break up into finer and finer portions so that we ultimately obtain a finely-divided emulsion like milk. In this condition the total amount of surface presented by the fat to the digestive action of the juice is very large, each little droplet contributing its share, so that the digestion of the fat can proceed as quickly as if the juice could soak into it.

The pancreatic juice contains also a very important enzyme that acts on proteins, or rather we should say, that continues the digestion of proteins begun by the pepsin in the stomach. For this protein-splitting enzyme of the pancreatic juice has not much action on the native proteins as they exist in the food; it is more specially adapted for acting on the peptones and other partially digested proteins that have been formed by the action of the gastric juice and passed over into the intestine. Under its influence these peptones are disintegrated completely—that is, they are broken down until their individual amino-acids are all separated one from the other. To continue the metaphor we used when speaking of the action of pepsin, we may say that by the action of the pancreatic juice the breaking down of the compli-

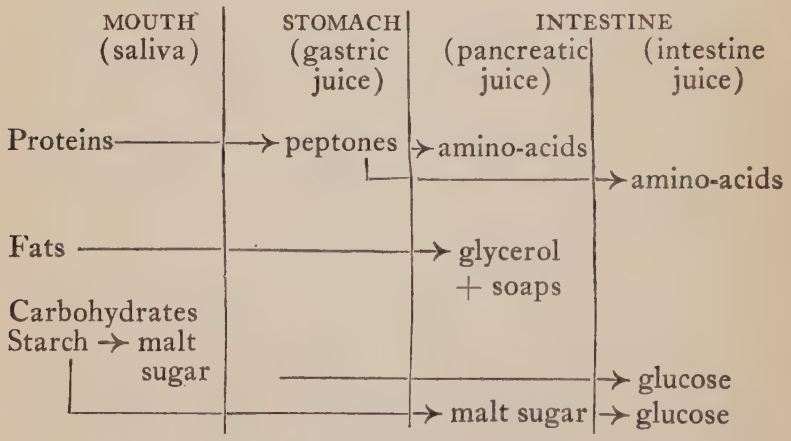
cated chains of amino-acids is carried on until all the individual links are separated.

Lastly, there is a third enzyme in the pancreatic juice—one which attacks starch. If the action of ptyalin were complete, this starch-splitting enzyme of the pancreas would have no material on which to act. But as a matter of fact, although, as the reader has been able to discover for himself, the ptyalin of the saliva acts so rapidly, it has not sufficient time to deal with all the starch that is likely to be included in a meal. For the length of time we give to chewing each mouthful is all too short, and although the ptyalin has some chance of continuing its action while the food mass lies in the stomach, it usually happens that the acid of the gastric juice will have soaked into the mass and stopped the action of the saliva before all the starch has been digested. The starch thus left over passes through the stomach without further change but is attacked when it comes into contact with the pancreatic juice in the intestine. The change there brought about in it is the same as that which occurs in the saliva: the starch is decomposed into sugar—malt sugar—in the way with which we are already familiar.

Powerful as the action of the pancreatic juice on all three classes of food-stuffs is, the digestion produced even by it is not complete. As the food is passed on into the more distant parts of the intestine it is still liable to contain a certain amount of protein not completely digested, i. e. a certain quantity of amino-acids not completely separated from one another. To meet such a possibility there is provided yet a further digestive juice which is formed by a large number of small glands situated in the inside lining of the intestine wall and poured on to the food through a large number of separate pores. This "intestine" juice has an enzyme for completing the splitting up of any protein fragments that have escaped the action of the earlier digestive juices, and also a set

of three more enzymes that act upon the more complicated sugars—malt sugar, milk sugar and ordinary cane sugar—and break these down, along the lines mentioned on p. 37 into their simple unit sugars.

This account of the digestive enzymes must seem to be a long story, but that is because there are so many of them and each must have a little attention. Let us now collect all that we have said about the digestion of the chief classes of food-stuffs into a kind of schedule. This will not tell the reader anything new, but it may serve to remind him of what we have already said:



From this table it will be clearly seen that in place of the proteins, fats and carbohydrates which are the constituents of an ordinary meal, we have in the intestine when the digestion of that meal is complete a mixture of amino-acids from the proteins, of glycerol and soaps from the fats, and simple sugars such as glucose from the starches and other carbohydrates. As soon as these digestion products are formed

they at once begin to soak or "diffuse" through the thin walls of the close network of little blood vessels which lie just below the inside surface of the intestine, and so soon as they are in the blood stream they are rapidly carried away and supplied to every part of the body. For the sake of exactness we ought to say that the digested fats do not pass straight over into the blood as do the sugars and amino-acids; they pass first into the little lymph vessels and only later when the lymph is all brought together into a larger vessel does it pass into the blood stream. As the food mass is churned up and pushed along by the muscles in the wall of the intestine this absorption of the dissolved products becomes more and more complete. The water that went to form the digestive juices is also absorbed and so is not lost to the body; for although we are land-living animals our tissues must be provided with an abundant supply of water. Water is therefore a valuable commodity in the body and must be used economically and not be wasted. In the end all we have left is the fraction of the food that has escaped digestion, together with such things as vegetable fibres and the cellulose walls of plant cells, for the breaking down of which we do not possess the appropriate enzymes. These residues, together with masses of bacteria that swarm in even the healthiest alimentary tract, go to form the waste or fæces which are, or should be, got rid of daily from the body.

It is interesting to think a little about this mixture of amino-acids, sugars, glycerol and soaps which form the end products of the digestion of an ordinary mixed meal. For although these substances form the end products of digestion they form at the same time the starting point from which the tissues begin to utilise the materials taken in as food. It is the simple sugars that are used as fuel, and it is from the amino-acids torn asunder during the digestion of the food proteins that the tissues build up their own new

proteins in the processes of growth or of maintenance. "But how is it," we might ask, "that if the tissues are going to use the proteins of the food for the production of their own proteins, it is necessary to break the food proteins right down into their constituent amino-acids and to start the synthesis of the tissue proteins from the very beginning in this way?" The answer to this question is that this seems to be, after all, the simplest way of bringing about the change. For although the proteins of the food and those of the tissues are composed of the same amino-acids, the proportions and arrangement in which these amino-acids are combined in the two types of protein are very different, and it is only by taking the first protein completely to pieces that we are able to build up from its constituents the new one. It is just as if we wished to re-arrange the links of a chain into a totally new order: the only way would be first to separate all the individual links and then to start with the re-arrangement; for the chance would be very remote that any two links that were adjacent in the first arrangement would be required to remain so in the second. There is no doubt that the breakdown *is* as complete as we have described, for the amino-acids have, by chemical tests, been detected in, and have even been separated out from, the blood of an animal during the absorption of a protein meal. And that the body can actually accomplish the linking together of separated amino-acids into its own proteins has been proved by an experiment in which a dog actually put on weight (that is, formed new "dog" proteins) during a period when it was receiving no protein food at all, but merely a mixture of amino-acids prepared in its master's laboratory. These facts will at all events help to explain how great is the importance of amino-acids—not merely as units of the chemical structure of proteins, but, further, as units of biochemical function, in the sense that they represent the stage to which all food proteins are

known to be broken down, and from which all new tissue proteins are formed.

Another point in the significance of this complete digestion of the food materials is that it results in the production of substances which the tissues can use. Living cells in general contain a surprising array of enzymes by means of which they are able to bring about a great variety of chemical changes useful to themselves. But the number of these enzymes is limited and it is obviously futile to supply to the tissues substances for which they possess no appropriate enzymes; for such substances could not, in general, be made to take part in any scheme of chemical change in the tissues and so would be useless for either the production of energy or the repair of wear and tear. This is very well illustrated by the behaviour of the sugars. It is only the simple sugars, like glucose, that the tissues can use: they have no enzyme capable of starting the chemical attack on so common a sugar, for example, as ordinary cane sugar, for if this is artificially injected into the blood it just circulates unchanged until it has all been filtered off by the kidneys into the urine. So that an individual with cane sugar in his blood is no better off than one who is starved of sugar; in fact he is, from some points of view, worse off because he has this foreign useless substance circulating in him. But when cane sugar is given, not into the blood, but in the ordinary way with the food, it meets in the intestinal juice (this is a point, we did just briefly mention on page 134) an enzyme that promptly breaks it down into glucose and fruit sugar, so bringing about the same change as we produce in the laboratory when we boil cane sugar with acid (see page 37). And both glucose and fruit sugar can be easily utilised in the body and burned completely to carbon dioxide and water. It will be remembered that an exactly similar digestion of milk sugar also takes place in the intestinal juice.

Lastly, it might be said that all these digestive enzymes with which we are provided protect us against many substances that would be very harmful if they arrived unchanged at our delicate tissues. Many substances that are perfectly good foods if completely digested by our enzymes are very poisonous if they get in an unchanged condition into our blood. In point of fact, proteins furnish us with our best examples in this connection. Quite a small quantity of a "foreign" protein can produce very grave symptoms and even lead to death if it is injected directly into the blood vessels, and yet the mixture of amino-acids obtained by the digestion of the same protein may be not merely harmless but of supreme use to the body in building up the tissues.

If we may retrace our steps a little, there is one further point we should like to make with regard to the way in which the various glands actually make their digestive juices. Before these things were at all well understood, the anatomists thought that a gland was a place where there were a large number of tiny holes in the blood vessels, and that when it poured out a juice this juice merely oozed through from the blood. But that this cannot be the case is seen at once when we know that each juice has its own particular composition and contains its own particular enzymes which are quite different from those belonging to the other juices. Moreover these enzymes are not to be found in the blood at all. To take a specific case, the blood is quite devoid of ptyalin and, for that matter, of the lubricating material mucin. It is evident therefore that the salivary glands cannot possibly be places where constituents of the blood just soak passively through tiny holes in the blood vessels. They are veritable little chemical factories. The blood brings to them not their finished products but only the raw materials from which they have to elaborate the characteristic constituents of their secretion by long and complicated processes of

synthesis. And so it is with the other glands. Stomach, pancreas, liver and intestinal glands are all the time carrying out similar but different processes of manufacture which result in the various enzymes and other agents we have mentioned. The gland cells usually work continuously at this process of manufacture and store up the finished product (or materials that can be quickly converted into the finished product) in the form of granules within themselves; there is thus a good stock of material ready for immediate secretion when there is food to digest and the active agents are required.

It is now time to finish this lengthy chapter. It has been long not because the subject itself is such an especially difficult one, but simply because we have had a great deal to say about digestion. Naturally it has taken us some time to give an account of the various stages through which the food materials are broken down before they are suitable for use by the tissues of the body; but in addition we have had to give the reader a very general account of those active substances called enzymes. For these agents are not merely responsible for the changes brought about during digestion —that in itself would entitle them to the fullest possible notice—but they are concerned in practically every chemical change that takes place in the whole realm of animate nature. Enzymes are universally present in all living matter, and they there bring about chemical changes that we can at once recognise as being useful to the organisms in which they occur. These changes are usually not inherently different from those we can produce when we experiment with non-living matter. Most of the "reactions" brought about by enzymes can be made to take place in dead materials in the laboratory. But the remarkable thing is that while in the laboratory we have to use boiling heat and violent reagents in order to bring about these changes, the enzymes can produce the same effects in the passive surroundings and gentle warmth of the body.

X

THE CHEMISTRY OF MUSCULAR EXERCISE

In introducing the subject of digestion we said that the details of the steps whereby the tissues use the digested materials carried to them are, for the most part, too complicated for general treatment. Nevertheless in this chapter we shall try to follow one particular line of these complicated changes: we shall consider, so far as we can, the processes that occur when a muscle burns up the fuel supplied to it and yields the energy by which its movement is brought about.

In earlier chapters we have said a great deal about the fuel and energy requirements of the body as a whole, and have many times pointed out how it takes fuel and burns it, giving carbon dioxide and water as its chief chemical products and mechanical energy and heat as its physical products. But even in its simpler manifestations the chemical process of combustion is in reality made up of a very complicated series of reactions, and the combustion processes that occur in living tissues form no exception to this statement. What we want to do now is to consider some of these reactions as they are found to occur in the body, and in order to do so we must study first the individual muscle and try to make out the events that take place between the moment when it is stimulated to contract and the slightly later moment when the effect of the stimulation has shown itself in the production

of movement and the liberation of the products of combustion. We shall do this with all the more interest, not merely because this is a fundamental question that has occupied the attention of physiologists and biochemists for a very long time, nor simply because it is a problem on which recent work has shed a great deal of light, but because it is one that has a very direct personal interest for us all, inasmuch as we are all the time using our muscles in the activities of both our work and our play.

Let us state our problem again for the sake of greater clearness. We have a muscle such as could be dissected from the limb of any one of us, although for both personal and scientific convenience we usually take it from the leg of a frog. When it is studied through the microscope it is found to consist of a large number of "muscle fibres" running from end to end of it. When it is stimulated suitably, say by giving it a tiny pinch or sending into it a weak electric shock, the fibres suddenly shorten and the muscle gives a twitch. The energy of this movement is known to come ultimately from a process of combustion, for the products of ordinary combustion—carbon dioxide and water—are set free from the muscle. What, then, can we find out about the actual chemical mechanism by means of which the muscle fibres are enabled to contract, and about the substances that are formed as intermediate steps between the fuel materials the muscle has burned up and the products of combustion it has produced?

It is not surprising that this question has occupied the minds of investigators from almost the earliest times, for, after all, movement is one of the most, if not the most, obvious of the characteristic properties of living matter. In order to find out if an animal is still alive we see whether it will move when we stimulate it with a touch or gentle blow. And then muscular movement is the one response of living

matter that is most easy to record and measure accurately. We have merely to attach to the muscle a light lever carrying a writing point that can move over a suitable recording surface (usually a slowly travelling band of smooth paper) in order to obtain a picture of the movements of the muscle and so to measure its activity as exactly as we please. Of course we cannot investigate thoroughly any process or phenomenon until we have succeeded in reducing it to number and measure; and this is very well illustrated by the case of muscular activity, for a great amount of our modern knowledge of this subject is the direct result of the employment of methods of measurement much more delicate and accurate than any that had been employed previously for the purpose.

Now as investigations have proceeded it has become clear that the problems presented by a twitching muscle are much more intricate than the earlier workers at this subject supposed. They held what seemed to be the most "natural" view—that the stimulus when it arrived "fired off," so to speak, the combustion in the muscle, with the consequent liberation of energy which manifested itself as movement. But when later it was discovered that a muscle can go on contracting even if it is cut off from a supply of oxygen, it became evident that in a muscle we are dealing with no ordinary process of combustion. The muscle can, for example, be cut out of the body and placed in a vessel filled with the inert gas nitrogen and yet we shall be able to get a twitch from it whenever we stimulate it suitably. In this way the muscle differs fundamentally from our ordinary combustion engines, for in these the energy production would cease at once as soon as the air supply was cut off and the fire in this way put out. However, the study of the body as a whole had already taught that the ultimate source of the energy produced in a muscle *is* a combustion process, so it is not sur-

prising to find that in order to take account of this new discovery the theory should have been put forward that a muscle is able to contract, even when it is not supplied with oxygen from outside, because it contains within itself some kind of store of oxygen sufficient for the carrying out of a certain amount of work. The idea was that the oxygen and the fuel material in the muscle were combined together in the form of an unstable complex that remained in the muscle fibres until, when a suitable stimulus arrived, it suddenly broke down into carbon dioxide and water with a sort of explosion that caused the actual contraction of the muscle. We use the word explosion intentionally here, for an ordinary explosive is just such a complex, being composed of a substance or mixture of substances containing combustible materials together with a supply of chemically combined but easily liberated oxygen sufficient for the instantaneous burning of the whole. When such an explosive is fired off it is the sudden liberation of large amounts of the products of combustion in the form of heated gases that produces the disruptive effects.

For a time after this theory had been put forward it did seem as if the analogy between a muscle and an explosive was a sound one, for even when the muscle is contracting in the absence of outside oxygen it gives off carbon dioxide, a characteristic product of combustion. A further fact that seemed to support the idea that a typical combustion process is taking place at the expense of a supply of oxygen that the muscle holds stored within itself is that in nitrogen, after a certain amount of stimulation, the muscle begins to respond more and more feebly until in the end it will not work any more—it is completely fatigued. But in order to restore it to practically its original strength all that is necessary is to give it a supply of oxygen for a while. Then when we replace it in the nitrogen it will contract as before every time we

stimulate it. This certainly does make it look as if the reason for the fatigue was the exhaustion of some internal supply of oxygen and that the recovery simply involves the replenishment of this supply.

But meanwhile a number of other important facts with regard to the chemistry of muscle had been accumulated. It had long been known, for example, that muscle tissues always contain a certain amount of *lactic acid,* a substance the name of which is derived like that of lactose because one of its forms is produced in milk when it turns sour. In this case it is produced by the action of bacteria on the milk sugar (lactose). The lactic acid that is found in muscle is not quite identical with that formed in milk but the differences between the two forms are very small and quite without significance to our present discussion. We might mention that as ordinarily obtained, lactic acid is a thick, colourless, syrupy liquid whose acid properties, for an organic substance, are really well marked. Now the amount of lactic acid that can be obtained from a muscle varies according to the treatment that muscle has been receiving. If it has been left at rest for some time before being analysed it will contain but little of the acid, but if it has been active just before the extraction a much larger amount of the acid will be obtained. It is evident, therefore, that this formation of lactic acid is closely bound up with the process of muscular contraction, and that any theory we make as to the mechanism of the muscle must take this important fact into account. But the "explosion" theory of muscular contraction just explained says nothing about lactic acid.

In order to obtain a better view of this important matter two English physiologists, Hopkins and Fletcher, undertook in 1907 a thoroughgoing investigation of the part played by lactic acid in the chemical economy of muscular tissue. These workers took two similar muscles—usually the correspond-

ing muscles from the two hind limbs of a frog—and placed one in a bottle of oxygen and the other in a bottle of nitrogen. The two muscles were then stimulated in the same way by means of electric shocks sent into them through suitably arranged wires, and their behaviours were compared. At the end of the experiment the amount of lactic acid that had accumulated in each muscle was determined by chemical analysis. The observations made in this way gave results of the highest importance for our understanding of this subject.

Hopkins and Fletcher found first of all that at the beginning the muscle that was in the bottle of nitrogen (and so cut off from an external supply of oxygen) contracted on stimulation as powerfully as its partner that was surrounded by oxygen, but that as the stimulation was continued the muscle in the nitrogen gave smaller and smaller contractions, until at last it failed completely to respond to the electric shocks, while the muscle in oxygen was contracting practically as vigorously as at the beginning of the experiment. The muscle therefore becomes much more rapidly fatigued when it is made to work without a proper oxygen supply. So far this is what was to be expected from the observations of earlier workers. But now came the important point: when the stimulation was discontinued and the amount of lactic acid in each muscle determined, it was found that the muscle that had been stimulated to fatigue in nitrogen contained much more lactic acid than the unfatigued muscle that had received all the oxygen it required during its activity. Evidently, then, the onset of fatigue is associated with the accumulation of lactic acid in the muscle.

When this had been established, the two experimenters went on to investigate what happens when oxygen is supplied to a muscle that has been completely fatigued by stimulation in nitrogen in this way. They found, as earlier workers had done, that the admission of oxygen removed

the fatigue so that the muscle was capable once again of giving contractions when it received electric shocks. At the same time they were able to show by comparison with a similar muscle that received no oxygen and so remained completely fatigued, that as the fatigue disappeared the accumulated lactic acid disappeared also. From this result they were at once led to ask whether the recovery of a fatigued muscle when it is placed in oxygen is really due, as the "explosion" theory would lead us to suppose, to the replenishment of a store of loosely combined oxygen in the muscle or whether it is not due to the removal by the oxygen of a product whose presence actually causes the fatigue—namely, the lactic acid. In other words, this observation threw doubt on the whole truth of the "explosion" theory.

Now once the theory had been called into question in this way it was natural to enquire whether other established facts about muscular contraction really fitted into it. We have already mentioned that the theory derives some support from the fact that carbon dioxide is evolved from a muscle when it contracts in nitrogen; so that there seems to be a combustion taking place in the muscle under these conditions. But, as we have seen, it is just under these conditions that lactic acid is formed most abundantly in the muscle. But muscle tissue is known to contain considerable quantities of carbon dioxide loosely combined as carbonates; and lactic acid is well known to be an acid strong enough easily to drive out carbon dioxide from carbonates outside the body. So here again we are faced with a question: might it not be that the carbon dioxide given off from a muscle during its contraction in the absence of external oxygen is, after all, driven out from the carbonates that the muscle already contains, by the lactic acid we know to be formed at the same time, and so is not necessarily the product of an explosion or combustion process at all? This point was also investi-

gated by Hopkins and Fletcher, and they found that the amount of lactic acid formed in a muscle contracting in nitrogen was easily sufficient to drive out from carbonates already existing in the muscle all the carbon dioxide that the muscle gave off during its activity. The establishment of this one fact was sufficient to prove that when a muscle contracts no combustion process necessarily takes place in it at the moment of its contraction, and so to render quite needless the, after all, somewhat unlikely theory that the muscle carries a store of loosely combined oxygen for the purposes of such a combustion. The "explosion" theory is itself exploded. The essential chemical change that occurs in a muscle at the moment of its contraction is the production of lactic acid and not the burning of fuel materials to carbon dioxide and water.

But let it be noted very carefully what we are saying here. We are not denying that the *ultimate* source of the energy of the muscular contraction is a process of combustion; the study of the whole body as a machine has proved that this is the case. The point is that the combustion does not necessarily occur at the same moment when the muscle is contracting and yielding its energy, but takes place during a later phase when the movement of the muscle is over and it has relaxed. The muscle behaves as if it were charged up with energy which it can release when it is suitably stimulated to do so. For this release no oxygen is necessary and during it no combustion process takes place. But once all the energy is released the muscle remains inactive no matter how much it is stimulated; it is completely fatigued and cannot yield up any more energy until oxygen has been admitted to it so that by a process of combustion it may replenish its energy stores and recover its activity. A muscle is in fact like a charged electric accumulator or storage battery; by suitable means we can take its energy and cause it to do useful mechanical

work for us, and while it is doing so it is quite independent of the oxygen of the outside air, for the chemical change that takes place in the accumulator during its discharge is not one of ordinary combustion. But once the accumulator is discharged we cannot obtain any more energy from it until we have lit a fire under a boiler—started a combustion process, in other words—in order to obtain energy for the turning of a dynamo and the production of the current necessary for the re-charging of the accumulator. As a matter of fact, under ordinary circumstances in the body the muscle is never completely cut off from a supply of oxygen, so that, even while it is contracting, a combustion process can start up within it and replenish the energy stores as they are being called upon. When in an experiment we first stimulate the muscle in nitrogen and then later admit oxygen to it for the purposes of its recovery, it is in order to show that the combustion *can* follow the active contraction and that the two processes are independent of each other, although under normal physiological conditions they are usually going forward simultaneously. The muscle in the body is actually more like the battery carried on an automobile and supplying current to the lamps at the same time as its energy is being replenished from the dynamo. But when the battery is being used to operate the starter of the car, it is more analogous to the muscle contracting in nitrogen, inasmuch as it is yielding energy that will only later be returned to it when the engine is running.

Without knowing any more than this about the chemical mechanism of muscular contraction we can see in this arrangement a kind of adaptation to a condition of life in which a sudden muscular effort might be at any moment required. The whole success of primitive man in defending himself against the attack of an enemy or in the capture of the beast that was to serve him as food, must often have de-

pended upon the promptness with which he could get his muscles into play, and it is obviously an advantage to possess muscles which, although deriving their energy ultimately from a process of combustion, will supply the energy first without waiting for the combustion to be got going, and then recoup themselves later when conditions of life are for the time being calm. But in this connection it must be remembered that the man's antagonist also possessed muscles working in the same advantageous fashion.

In describing this production of lactic acid we have explained the most important point in the chemistry of muscular contraction as we know it to-day. But in doing so we have raised far more problems than we have solved. From what is this lactic acid produced? how does it cause a muscle fibre within which it is liberated to contract and pull? and what happens to the acid when oxygen is admitted to the muscle? It disappears from the muscle, but into what products is it converted? Let us take these points in logical order and begin by considering the origin of the lactic acid.

In Chapter III, the reader may remember, we mentioned a substance called *glycogen*—a kind of starch that is stored as a reserve material in the bodies of animals and mainly in their livers and muscles. Under usual circumstances the total amount of it in all the muscles of the body together will be about equal to the amount in the liver, but this will be a variable quantity as it depends on the amount of food the animal has received before being examined. It also depends on the amount of muscular activity that the beast displays, for careful analyses of the amount of glycogen in a muscle under various conditions of activity have shown that when the muscle contracts and lactic acid is produced in it, its stored glycogen is diminished in amounts corresponding to the acid formed. It is evident therefore that the lactic acid has been formed from the glycogen. From

the point of view of the chemist there is nothing very difficult about such a reaction. Glycogen is, as we have seen, a carbohydrate, and lactic acid, as it happens, contains carbon, hydrogen, and oxygen in the same proportions in which they occur in the carbohydrates. Yet in order to convert the one substance into the other it is necessary to pass through a number of intermediate steps.

That this explanation of the origin of lactic acid in muscle is the true one has been confirmed by quite another line of reasoning. By direct physical observation, using the bomb calorimeter, it is possible to measure how much energy is liberated when 1 gm. of lactic acid is formed from glycogen in the laboratory. By taking a muscle and mounting it in a delicate calorimeter in such a way that when it is stimulated it cannot shorten but can only pull on its fixed supports, all the energy that it produces during a certain period can be converted into heat and so measured. The amount of lactic acid produced as a result of the activity can also be determined by analysis of the muscle at the end of the experiment, provided, of course, the calorimeter is kept filled with nitrogen so that the lactic acid produced remains in the muscle and is not removed as it would be if oxygen were present. From these figures we can then easily calculate how much energy is liberated when 1 gm. of lactic acid is formed in the muscle. And when these two values are compared it is found that, provided the exact conditions under which the lactic acid finds itself in the muscle are taken into account, the amount of energy associated with the formation of a gram of lactic acid in the muscle is as nearly as possible the same as the amount we should expect from experiments on the interconversion of these substances outside the body. These experiments (which, incidentally, have been carried out with great exactness, the little calorimeter used for the muscle being sensitive enough to record a change in its temperature

of less than one millionth of a degree) leave no doubt at all that it is from the stored glycogen of the muscle that the lactic acid is produced, and that the immediate source of the energy which the muscle puts out during its contraction comes from the chemical reaction which we can express as follows:—

glycogen ⟶ lactic acid

Now the question arises as to what happens to the lactic acid when the contraction of the muscle is over and it is using oxygen during its recovery phases. The acid, as we have already mentioned, disappears from the muscle—but where to? This question has been much debated, for there were several possible answers that were difficult to choose between until it was discovered that when a fatigued muscle absorbs oxygen, as its lactic acid disappears its glycogen content increases again. As this re-formation of glycogen goes hand in hand with the removal of the lactic acid it is now thought that during the recovery phase in the muscle the above reaction is reversed and we now have:—

lactic acid ⟶ glycogen

At one time it was thought that all the lactic acid that had been liberated in the muscle was built back into glycogen in this way, and this gave rise to the statement that "the lactic acid is part of the machine and not part of the fuel." Of course, seeing that the formation of lactic acid from glycogen gives us energy, the reversal of the process and the re-formation of glycogen require the supply from outside of just the same amount of energy—otherwise we should be obtaining energy for nothing, which is contrary to all human experience. So that during the period of recovery of the muscle *something* must be burned in order to supply this energy: indeed, this is the period during which combustion

occurs in the muscle. We now know that what is burned during this period is a certain fraction of the lactic acid itself. Only about three quarters of it is actually built back into glycogen, the remaining quarter undergoing complete combustion to carbon dioxide and water. The burning of this fraction of the lactic acid yields sufficient energy for the building back of all the rest. It is easy for us now to make these statements in a few short sentences, but it should be realised that the establishment of these fundamental points in the chemistry of muscle required a great deal of careful and patient work.

The whole process of the chemical changes occurring during the cycle of a muscular contraction may, then, be regarded as made up of two distinct phases, one in which, as a result of the stimulation, glycogen suddenly breaks down, yielding lactic acid, which in some way causes the muscle fibres to contract, but without the occurrence of any combustion process; and the other in which the energy yielded during the first phase is restored to the muscle by the combustion to carbon dioxide and water of a certain fraction of the lactic acid that has been liberated, the remainder of the acid being reconverted into glycogen. There we will leave the matter at the moment, for we have yet to say how the lactic acid formed in the muscle causes it to contract and pull. Or rather, we have yet to mention the theories that have been put forward to explain this link in the complicated chain of events that takes place each time we even so much as twitch a finger; for although we have now a considerable amount of information as to the way in which the lactic acid is suddenly produced in the muscle, we have not many facts to guide us in deciding its mode of action when once it has appeared.

In the first place, however, we know that when a muscle contracts its total volume does not alter, so that the

act of contraction consists fundamentally of a change in the *distribution* of the material of which the muscle is composed. It has been supposed that the tiny threads that actually do the pulling in a muscle fibre are enclosed in a thin skin or membrane, inside which the lactic acid is formed. This would cause water to pass in from the outer material of the fibre through the membranes into the threads, making them bulge and shorten. We are certainly well acquainted with this kind of process: water will usually pass through a membrane into a solution of a salt or acid or similar substance inside by what chemists call *osmosis*. It can be very easily illustrated by taking an ordinary animal bladder (not an artificial rubber one as indiarubber is impermeable to water) filling it just loosely with a strong solution of salt and then lowering it into a large vessel of water. The water will pass in through the bladder until it is filled quite tight and stretched; it can even be caused to burst by such means. But so far as muscle is concerned there is only a possibility that this kind of thing takes place on a small scale in its active structures: it has not been proved. Another possibility that has been suggested is that these active structures just swell up and so shorten, in the same way in which a piece of gelatine or violin string is known to do when placed in an acid solution. Yet another very favourite idea has been that the lactic acid liberated in the muscle threads increases what the physicists call the "surface tension" of the surfaces of these threads and so causes these surfaces to shrink, that is, to contract. But it has been calculated that the amount of lactic acid formed in one twitch of a muscle is not sufficient to cover even with the thinnest possible layer more than a small fraction of the total area of all the contracting threads that can be seen in a muscle under the microscope. The present idea is, therefore, that the acid in some way changes the arrangement of the particles in these

surfaces and causes them to turn from a lengthwise end-to-end arrangement into a more or less side-to-side position, and as these particles are known from other observations to be longer than they are broad, this would account for the shortening of the thread of which they form constituents. We cannot go into further details of these speculations here, but we have probably said enough to show the reader what a lot we have yet to discover before we can claim to know at all completely all that takes place when he merely raises his little finger or blinks his eye.

So far we have dealt only with the events that occur during the activity of a single muscle or indeed of a single fibre of a muscle. But this leads us naturally to enquire what applications this knowledge can have to the study of muscular exercise involving the body as a whole. We have in previous chapters said quite a good deal about the body at work, but now that we know something about the mechanism of the contraction of a single muscle there are some further points at which we can get a deeper insight into the working of the whole individual. For many of the facts that are true of a single muscle must of course also be true of a group of muscles working simultaneously. Just as the single muscle gives us energy first and then afterwards absorbs the oxygen necessary for the subsequent energy-replenishing combustion, so also it is found that the body as a whole at the beginning of a spell of muscular work absorbs much less oxygen than corresponds to the rate at which it is working. It is therefore yielding energy before the combustion necessary for the replacement of that energy has been got under way. In principle this is very easy to prove: all that is necessary is to get the subject of the experiment to breathe into a bag while he starts up the work, which, for convenience, may consist in pedalling on the stationary bicycle. Then by analysing the air in the bag from time to time one can determine

the rate at which oxygen is being used up from it, and it is found that although the muscular effort may start at once with its maximum intensity at the signal "go," the rate of absorption of oxygen increases only slowly and may take several minutes at least before it corresponds with the amount of oxygen that must be absorbed per minute in order, by bringing about the combustion of fuel, to supply energy at the rate at which the subject of the experiment is using it. But the energy which is thus at the outset of the work provided free must ultimately be restored to the muscles if the body is not to be permanently exhausted by its first effort. And as a matter of fact we find that when the work stops the increased rate of oxygen absorption does not stop simultaneously with it, but continues into the subsequent period of rest, until all the extra oxygen that the body did not take in at the beginning of the work has been absorbed. Everyone knows that we remain out of breath for quite a long time after stopping a vigorous effort. Now from what we have said about the individual muscle it will be readily realised that this extra oxygen absorbed during the paying off of what has been called the "oxygen debt" of the body is used for burning up a certain fraction of the lactic acid that remains in the muscles at the end of the work. We can therefore see that the amount of oxygen debt will be a measure of the amount of lactic acid to be removed.

Now the amount of lactic acid that accumulates in a man's muscles during a given amount of exercise will depend on two chief factors: one will be the rate at which the acid is being *produced* (and this will depend in turn on the severity of the work); the other will be the rate at which the acid is *removed* during the work, and this will be determined by the rate at which oxygen can be transported to the muscles for the purpose of the removal of the acid, this, in turn, being determined by the efficiency of the whole of the man's respi-

ratory and circulatory systems. But the extent to which lactic acid accumulates in this way during muscular work would not matter very much (provided the glycogen supply was adequate to meet the needs of the muscles) were it not for the circumstance that the lactic acid, when it has reached a certain concentration, does not all stay in the muscles; some of it begins to diffuse out into the blood. In this way it passes to all parts of the body, and being a somewhat strong acid it produces those harmful effects known as acid poisoning or *acidosis*. The blood and tissues contain alkaline salts that neutralise to a great extent these harmful acid properties but they do not remove them altogether, and if the muscular effort is so severe that the blood and tissues continue to become more and more acid as the work proceeds, this accumulation of lactic acid produces the feeling that one can go no further and finally brings the body to rest in a condition of exhaustion. The fainting athlete gives up, not because his heart or lungs are working less efficiently than earlier in the effort, but because his body has accumulated more lactic acid than he can stand. Now in grading men according to their athletic abilities it is evident that this is exactly what we want to know—how far the particular individual can go with a muscular effort before he will be exhausted. And it is evident also that this consideration of the oxygen debt gives us a means of obtaining this information. We cannot analyse the man as we could a piece of muscle cut out of the body of a frog; nevertheless we can get an idea of the amount of lactic acid he has produced during a certain spell of exercise by determining the amount of the oxygen debt that he has to pay back at the end of it. Roughly speaking the less oxygen debt he incurs for a given effort the more reserve he has available to draw on when the effort is more severe. By investigating a man in this way we do not make of him a better athlete but we do derive information

as to what his standard of athletic performance is likely to be. The changes that we produce in him when we do try to improve his athletic performance—when we take him into training, that is—are complex. We feed him well and so ensure that his tissues have abundance of material with which to maintain the maximum amount of active living stuff, and at the same time we give him practice in carrying out the particular movements required in his sport so that he comes to carry them out most economically, that is, with the use of the least possible number of muscles, and so with the lowest possible consumption of material and the minimum production of fatigue.

The total amount of lactic acid liberated in the body during muscular work is really surprisingly large: it may amount to several ounces. The reader, even if he is not given to vigorous athletic activities, must certainly be familiar with its effects. He must know the stiffness that follows any unusual amount of muscular exertion, and as he stretches himself to get his muscles relaxed he will realise that this stiffness is due to a long-continued contraction caused by the lactic acid they still contain. As is well known, a very effective way of preventing or removing stiffness is to take a hot bath as soon as possible after the exertion: this is because the warmth opens up the blood vessels and, by increasing the rate at which blood is supplied to the muscles, permits the more rapid and complete removal of the lactic acid.

From all we have said it will be realised that when a muscle has carried out a certain amount of work, and has then recovered from the consequent fatigue, the net change produced in it is that its store of glycogen is smaller than at the outset. It will be appropriate, therefore, here to consider the ways in which the glycogen stores of the muscles are replenished during periods of rest, and to refer again to the general question of the storage and transport of reserve fuel mate-

rials in the body. The combustion processes are going on continuously in the body, although of course more vigorously at some times than at others. But we eat—that is, take in new supplies of fuel—only intermittently, so it is evidently very necessary that there should be some means whereby we can store excess of fuel materials and distribute them to active organs as they are required. There are, as a matter of fact, several ways in which the reserve materials are stored in the body.

The sugar we eat, and also that obtained by the digestion of the more complicated carbohydrates, is absorbed from the alimentary canal into the circulating blood. Now it is a very important anatomical fact that the blood that leaves the alimentary canal all passes through the liver before it gets into the general circulation. Here in the liver the excess of sugar that the blood contains is converted into glycogen and stored in this form. That is while food is being digested in the alimentary canal. But between meals, when the muscles are using up their glycogen and no new supplies of material are coming in from the outside, the reverse process takes place. The glycogen of the liver is broken down again into sugar by means of an enzyme and this sugar passes into the blood and so can be carried round to the muscles that are being active. Here it is easily absorbed and is used for making new glycogen so that the supply of this substance which is, so to speak, the starting point of the chemical changes taking place during muscular contraction, is maintained. This may seem to be a rather roundabout process but actually we can see a great deal of significance in it when we consider the respective properties of sugar and glycogen. Glucose, the sugar we are dealing with in this connection, is a relatively simple substance that readily diffuses through animal membranes and cells, so that if a large amount of it got into the general circulation by absorption from the alimentary canal

it would pass through the membranes of the kidney and so come to be wasted in the urine. As it is, the liver catches it and deposits it in the form of glycogen, which, although soluble, is a sufficiently complex substance to be held back by membranes. Then, when more fuel is required by the muscles, this glycogen is broken down again into sugar and let out into the blood, but in such small regulated quantities as the kidney can keep back. The muscles can therefore absorb it and use it in the way we have described. We might mention again that glycogen is formed in the liver not merely from sugars coming from the alimentary canal, but also from some of the amino-acids obtained by the digestion of proteins. In this way we can understand how any excess of protein we eat over and above the amount that the tissues require for their maintenance is also used as fuel. In this formation of glycogen the nitrogen of the amino-acid has to be removed; it goes to help form the urea of the urine.

Another way in which the body stores reserve fuel material is in the form of fat. This may come directly from the fat we eat with our food or may be produced by chemical transformation of some of the sugar. Fat is a very economical fuel material to store because it contains such a small proportion of oxygen—much less than that contained in glycogen, sugar or other carbohydrates. So that we have relatively a much greater proportion of combustible carbon and hydrogen in a given weight of fat than we have in the same weight of glycogen. We can compare fat with oil fuel and glycogen with coal, and point out that there is much less room wasted with air spaces in a tank of oil than there is in a bunker of coal. We thus see how it is that in Chapter V we found a gram of fat to be capable of yielding more than twice as much energy in the body as a gram of either carbohydrate or protein. Although there is no doubt that fat is also ultimately used as a source of muscular energy in the

body we do not know very much at the moment as to the way in which this takes place. It seems most likely that the fat is first converted into sugar and that this is then used by the muscles in the same way as sugar derived from any other source.

XI

BLOOD AND IRON

Now let us carry our minds back for a moment to what we were saying about the chemical changes taking place in the body during muscular exercise. We have seen that the essential feature in the chemistry of muscular contraction is the production of lactic acid; that during the recovery phase a very considerable fraction of the amount of this acid at first liberated is reconverted into glycogen by means of energy obtained by the burning up to carbon dioxide and water of the rest of the acid; but also that the more severe the exercise the more does this process of oxidative removal lag behind the production of the acid which therefore accumulates in the body and leads to the fatigue that ultimately brings the muscular effort to an end. Now the muscles have always a good supply of glycogen from which to produce lactic acid and they keep this supply replenished from the sugar they absorb from the blood. The factor, then, which limits the amount of muscular work that the body can carry out without rest is not the rate at which lactic acid can be produced but the rate at which it can be removed from the muscles, and, as we have just said, this removal requires oxygen. It is therefore the rate at which oxygen can be supplied to his muscles that determines what we may call the "horse power" of a man.

Now it is not very difficult to understand that this trans-

port of oxygen from the outside air to the active muscle fibres deeply embedded in the compact mass of the body presents a serious problem in the economy of the animal organism. In the case of the tiniest animals this problem does not exist as, owing to their minute size, no part of their living matter is very far from the surface: all parts are therefore within easy reach of the oxygen that soaks or diffuses through the surface of the animal from the medium (usually water) in which it lives. But as soon as we come to larger animals, and particularly when we think of those that possess a thick protective skin, we realise that the problem of the transport of oxygen to the internal tissues of the body requires more elaborate means for its solution. In insects the air is carried directly to the internal tissues by means of a complex system of air tubes which branch and divide again and again until it comes about that practically every muscle fibre receives its own little pipe line supplying it with the oxygen it needs. Apparently this arrangement is one that is capable of considerable efficiency, for not only does it serve the needs of our comparatively small modern insects but it must have sufficed to convey an adequate supply of air to the muscles of the giant dragon flies measuring as much as two feet across the wings that we know from their fossil remains to have existed in the rocks of what the geologist calls the carboniferous period.

Nevertheless, this is a relatively unusual arrangement of the oxygen supply. In practically all other animals the oxygen is carried from the outside air or water to the active tissues of one kind or other in the blood. The oxygen is taken up in a special part of the body where this blood is separated from the outside medium by only a very thin membrane through which the oxygen can soak easily and therefore quickly enough to supply the animal's needs. This is what happens, for example, in the lungs of land-dwellling animals

like ourselves, and in the gills of fishes and other inhabitants of sea and river. From their very nature it is obvious that gills and lungs are extremely delicate organs, and we find them usually well protected by gill covers or a bony cage of ribs, as the case may be. The blood is propelled through the maze of tiny thin-walled "capillary" (i. e. hair-like) blood vessels in these respiratory organs by the muscular activity of the heart. When it arrives at the various tissues of the body the blood finds itself again in a network of capillaries, through the thin delicate walls of which oxygen can now easily pass out to the active cells in the neighbourhood. To take a specific instance, it is found by microscopic study that each individual muscle fibre in a muscle has running beside it its own little capillary blood vessel from which it is supplied with oxygen in this way. But all this belongs to the realms of physiology and anatomy. What interests us more particularly as biochemists is not so much the detailed arrangement of the blood vessels supplying the various tissues as the nature of the changes that take place in the blood when it absorbs the oxygen in the lungs and when it later unloads this oxygen in the organs of the body where it is required.

It was known to Priestley a century and a half ago that ordinary blood, which is dark purplish when first shed, turns colour and becomes bright scarlet when it is exposed to the air. It is, further, a matter of common experience that while the blood we lose from ordinary pricks and superficial cuts has this dark purple colour, the blood that squirts out when as a result of a deeper injury an artery is severed, has the bright scarlet colour of blood that has been in contact with air. Indeed it *has* been in contact with air, for the blood in arteries is that which has just passed through the lungs and is on its way out to be distributed to one or more of the organs of the body. It is loaded with oxygen. On the other

hand, the blood from ordinary little cuts comes from small veins through which it is passing back towards the heart and lungs after having unloaded the greater part of its oxygen in some active organ or other. Thus we see that the colour of the blood depends on the amount of oxygen it contains: the richer in oxygen the redder it is, the poorer in oxygen the bluer it appears.

The red material that is present in such conspicuous amount in blood is therefore very intimately concerned with the power of the blood to carry out its function of transporting oxygen from the lungs to the other organs of the body. This red pigment is called *hemoglobin*. It is to the presence of a large amount of this substance that the blood of every vertebrate animal owes its colour. Not many invertebrate animals contain it but there are a few—among others some insect larvæ and a certain number of worms—that do, and of these the common earthworm is one. In vertebrate animals generally the hemoglobin is not just simply dissolved in the blood fluid, but is contained in an enormous number of tiny cells or corpuscles which float in an almost colourless liquid called the blood *plasma*. Roughly speaking, we may say that about half the volume of the blood is made up of corpuscles and half of plasma; but so tiny are the individual corpuscles that a drop of blood of the size of a pin's head contains about five millions of them.

When blood is allowed to stand undisturbed the corpuscles slowly separate from the plasma and sink to the bottom of the containing vessel, but a much more complete separation is obtained by the use of a centrifuge—a machine that runs on the same principle as a milk separator. When tubes of blood are spun around in such a machine at a high speed —anything from two to ten thousand revolutions a minute—the corpuscles are driven down to the bottom of each tube and can be obtained as a compact mass free from plasma.

Then by various simple methods it is possible to break up these corpuscles and to cause them to set free the hemoglobin they contain. In this way a solution of hemoglobin can be obtained and if this solution is strong enough we can get solid hemoglobin from it in the form of a mass of red crystals.

Now seeing that this pigment hemoglobin is the substance responsible for the transport of oxygen in the blood, it is evidently a very important thing to know as much as possible about the way in which it carries out this important function. When we make a solution of hemoglobin in the way we have outlined we usually do not bother to protect our solutions from the air during our manipulations and so the hemoglobin solution will have had abundant chance of taking up as much oxygen as it will. And the fact that it has taken up this oxygen is shown by its bright scarlet colour. Now we can get back all the oxygen that the hemoglobin solution has taken up in this way by merely exposing the liquid to a vacuum, that is, by shaking it in an apparatus from which we have pumped all the air. As the gas bubbles off a great deal of frothing occurs but by using suitable apparatus this can be prevented from causing inconvenience, and the liberated oxygen can be collected and measured. If we do this with a solution containing about ten or twelve per cent of hemoglobin, which is about the amount present in the blood, we find that for each 5 volumes of solution we obtain 1 volume of oxygen. This in itself is a very important result because it shows what a large amount of oxygen can be taken up by each drop of blood and given off again when the blood is put into a vacuum, i. e. a space where there is no oxygen. If instead of using this hemoglobin solution we had taken plain water and first saturated it with air and afterwards exposed it to the vacuum, we should have found that it would have dissolved and then later given up again a quantity of oxygen amount-

ing to only about one fiftieth of the amount that the hemoglobin solution absorbed and gave up. It goes without saying that if a fluid is to be used for the efficient transport of oxygen it must be capable of absorbing and of giving up again large quantities of the gas, and these figures illustrate how superior solutions of hemoglobin, and among them blood, are in this respect to plain water. Blood is indeed "thicker than water." We can express the matter in another way by saying that the more oxygen each drop of blood is capable of carrying, the smaller the quantity of blood that need be pumped round the body each minute in order to supply the oxygen needs of the tissues.

Thus we begin to realise how important a substance hemoglobin is in the blood. But we cannot appreciate its importance to the full until we have studied in more detail the way in which it takes up the oxygen in such relatively large quantities. For one thing, the conditions under which the hemoglobin finds itself in the body are rather different from those that obtain in the experiments we have just described. Certainly in the lungs, owing to the continuous ventilation brought about by the rise and fall of the chest during breathing, the blood is exposed to air that contains not much less oxygen than the ordinary air of the atmosphere. Of course there will be *somewhat* less oxygen than in the atmosphere because the blood is all the time absorbing it; but the difference is not great. But in the body the blood is never at any time exposed to a vacuum; it never gives up the whole of its oxygen in the way we have imagined in our experiment. By the time, for example, that it has traversed an active limb and appears in the veins that conduct it back to heart and lungs it has rarely given up more than half of the oxygen with which it set out along the arteries.

In order therefore to study the transport of oxygen in the body and in order to obtain full information about the way

in which hemoglobin takes up and gives off oxygen, we must not merely expose our hemoglobin solution to ordinary air and then to a vacuum, but we must fill in the gap between these two extreme conditions by determining how much oxygen the same hemoglobin solution will take up when exposed to a number of different pressures of oxygen somewhere between 0 (which is the oxygen pressure in a vacuum) and the pressure of oxygen in the atmospheric air. The simplest way of doing this is to make up in a series of closed glass vessels a number of mixtures of some inert indifferent gas, such as nitrogen, with various proportions of oxygen, exposing separate portions of the hemoglobin solution to these various gas mixtures until the hemoglobin has taken up all the oxygen it will. The nitrogen used in such an experiment exerts no influence on the hemoglobin; it merely serves to dilute the oxygen to the desired concentration. When, as the chemists say, "equilibrium has been established" between the portions of hemoglobin solution and the gas mixtures, the solutions are carefully withdrawn and the amount of oxygen each contains is determined in some suitable way, say by removing and collecting the gas in a vacuum pump. When the results of all these analyses are brought together we have a collection of data from which we can at once say how much oxygen a given amount of our hemoglobin solution will contain when it has been exposed to any given concentration or pressure of the gas, and when we compare all the figures we find that, as we should expect, at very low pressures of oxygen the amount of gas taken up by the hemoglobin is very small, but that as the pressure of oxygen is increased the amount taken up by the hemoglobin also increases —at first very markedly (so that a small increase in the oxygen pressure to which the hemoglobin is exposed leads to a large increase in the amount of oxygen taken up) but then more and more gradually until, when we come to deal with

pressures of oxygen about equal to that which exists in the atmosphere, the amount of oxygen taken up by the hemoglobin hardly increases at all as we increase the pressure. The hemoglobin is then, as we say, "saturated" with oxygen. It is important to realise that these measurements tell us not only how much oxygen will be taken up under any conditions by a solution of hemoglobin that at the beginning contains none of the gas, but also how much oxygen a hemoglobin solution originally saturated with the gas will lose when exposed to a given gas mixture. For no matter whether we start with a solution of hemoglobin containing no oxygen, or whether we start with one already saturated with the gas, the solutions will finally come to contain each the same amount of oxygen after they have been brought into equilibrium with the same gas mixture.

Now the results of such experiments are very important to the physiologist who wishes to know exactly all the conditions that determine the rate at which oxygen can be transported in the body. But they are important also to the biochemist, for they shed light on a problem that has attracted a very considerable amount of attention among those who are interested in these things—the problem, namely, of the nature of the union that takes place when, as we have said, hemoglobin "takes up" oxygen. There are, in fact, two main possibilities. Firstly, the hemoglobin and the oxygen may unite *chemically;* that is, when they come together an entirely new substance, a compound of the two, may be formed; or, secondly, the union may be a mere *physical* one in which the hemoglobin and the oxygen become, as it were, intimately mixed but still exist in the mixture as separate particles of oxygen and hemoglobin, so that no new kind of material is produced. Between these two alternatives it is now possible to decide, for the laws obeyed by substances when they unite chemically are well known, and so also are those that govern

the various forms of physical union. From these laws it is not so very difficult to calculate how much oxygen a hemoglobin solution should take up at various pressures of the gas, first on the assumption that the combination is chemical, and secondly on the assumption that it is physical. We obtain different answers in the two cases. Now all we have to do is to see which of the two answers agrees with that which we actually find by experiment. When we do so we find that the experimental results agree much better with the calculations made on the basis of a simple chemical combination than with those made on the basis of a physical union, and so we conclude that a chemical process is involved. What this means is that the bright scarlet stuff produced when hemoglobin combines with oxygen is an essentially new material or compound differing very markedly in its properties from the two materials, or from a mere mixture of the two materials, from which it is formed. Being a new material it deserves a separate name and so it is called *oxyhemoglobin* to remind us of the mode of its formation.

We can therefore now say that when blood takes up oxygen in the lungs its hemoglobin combines with the oxygen to form the new chemical compound, oxyhemoglobin:

$$\text{hemoglobin} + \text{oxygen} \longrightarrow \text{oxyhemoglobin}$$

and that when the oxygen is in turn given off to the tissues that use it the oxyhemoglobin breaks up or decomposes once again into its constituents:

$$\text{oxyhemoglobin} \longrightarrow \text{hemoglobin} + \text{oxygen}$$

Now these chemical changes are very interesting indeed because there are very few in the whole of chemistry like them. It is this that makes hemoglobin so unique and fascinating to study. The point is that we know many many substances that will combine chemically with oxygen but we

know practically none that forms a compound that will split up so readily as will oxyhemoglobin and give up the oxygen again. And, let us repeat,—a substance that is to be of use for the transport of oxygen must be able not only to combine with oxygen in the place from which the oxygen is to be transported, but also to liberate the oxygen again in the place where it is required. One of the commonest examples of a chemical combination with oxygen is seen when a piece of iron rusts. The rust is a chemical compound of the metal with the oxygen that is absorbed from the air. But this compound would be of very little use for the transport of oxygen under the conditions found in the blood, for once formed it is very stable and only by extreme measures (such as by heating it with carbon in a blast furnace) can it be induced to part with the oxygen again. Hemoglobin will not merely combine with oxygen from the air in the lungs but it will consent to give up this oxygen again under the conditions that prevail in the tissues of the body. The only reason why oxyhemoglobin breaks up into oxygen and hemoglobin as the blood passes through an active organ is that this is a place where oxygen is being very rapidly used up for the burning of fuel materials so that its concentration here comes to be very small. We have already seen that when hemoglobin is exposed to only a small concentration of oxygen it combines with only a small amount of the gas, or—what comes in a very literal sense to the same thing—when oxyhemoglobin is exposed to such a low concentration of oxygen it splits up to a greater or lesser extent into oxygen and hemoglobin, and the actual amount of oxygen that the hemoglobin takes up or with which it remains combined is determined only by the pressure or concentration of the oxygen which prevails. The greater the concentration of oxygen, the greater the proportion of oxyhemoglobin that remains; the lower the oxygen concentration, the greater the amount of hemoglobin

that lets its oxygen go. In the lungs we have a high concentration of oxygen because the movements of breathing are all the time pumping fresh air in and used air out; in the tissues of the body we have a low concentration of oxygen because this gas is used up during combustion.

This is a very instructive case of what is called *chemical equilibrium*. It is not difficult to understand the way in which the chemist pictures to himself what is happening in such a case. He regards the particles of oxygen and hemoglobin as being in continuous rapid movement in the solution in which they are present together. When a particle of hemoglobin and a particle of oxygen come together with sufficient force they unite to form a particle of oxyhemoglobin, but while this is going on some of the partnerships already formed are being broken up again, some of the particles of oxyhemoglobin quite spontaneously fall to pieces, and the oxygen and hemoglobin particles are once again free to enter into other combinations, according as the chances and opportunities of their ceaseless dance permit. Thus in a solution that contains hemoglobin and oxygen together we picture two processes going on at the same time—a continuous combination of hemoglobin particles with oxygen to form particles of oxyhemoglobin, and a simultaneous breaking up of some of the oxyhemoglobin already formed into oxygen and free hemoglobin. Now it is easy to see that the amount of oxyhemoglobin present in the solution at any particular instant will depend on the relative rates at which these two processes are going forward. If the combination of the two constituents is occurring quickly and the breaking down of the oxyhemoglobin is going on only relatively slowly, then there will be a large proportion of oxyhemoglobin present; but if the combination is going on slowly and the breaking down quickly, most of the oxygen and hemoglobin will be at any moment uncombined.

Now, as a matter of fact, the breaking up of oxyhemoglobin into its constituents being, as it were, a spontaneous process, will be but relatively little affected by outside circumstances. It is as if the combination between the two constituents were capable of lasting only for a limited time, after which re-separation occurs. The total amount of oxyhemoglobin breaking down during any given short interval of time will simply depend on the total number of particles of oxyhemoglobin present in the solution at the beginning of that time interval. But with regard to the rate of combination of the oxygen and hemoglobin, the conditions will be rather different; for here we have two kinds of particle involved, and two particles, one of each kind, must happen to come together in order that combination shall occur. The chance of their doing so—or, what is the same thing, the rate at which they will do so—will depend entirely on the number of each present in a given space, in other words, on the concentration of each, and thus we can understand how it is that the amount of combination taking place, that is of oxyhemoglobin formed in a solution, increases as we increase the pressure or concentration of oxygen in the solution, until finally, when the concentration of oxygen is really high, as when the solution is exposed to atmospheric air, a particle of hemoglobin has practically no chance of remaining uncombined and the conversion to oxyhemoglobin is to all intents and purposes complete.

All this may seem complicated but it demands only a little clear thinking in order to be understood. Perhaps it may help if we very briefly suggest an analogy and ask the reader to imagine what happens when on a hot summer day the bees are swarming round the flowers in a garden. We will suppose that each bee represents a particle of oxygen and each flower a particle of hemoglobin. At the time when the bees come into the garden we can imagine that every flower

is unoccupied, but as in the course of their wandering flight the bees come into contact with them, more and more of the flowers become occupied—in other words, combination occurs—and, obviously, the more bees there are about, the more combinations are formed in the first few seconds. But soon some of the first bees to combine grow tired of their particular flowers and leave them in order to fly freely again in search of others. Here we have the breaking down process setting in, and again, evidently, the number of breakdowns that can occur during any second of time must be in proportion to the number of combinations present at the beginning of that second. At first, of course, the number of combinations will be in excess of the number of separations but gradually, as the number of unoccupied flowers becomes smaller, the rate at which further combinations occur diminishes, for it gets harder and harder for a bee to find an unoccupied flower. But meantime, as the number of combinations increases, the chance of an already formed combination breaking up is getting larger and larger, until at last we arrive at a stage where the increasing rate at which separation occurs just balances the diminishing rate at which new combinations are being formed, where, in other words, we have a condition of equilibrium. The number of bees finding new combinations in a given second will then be just equal to the number of bees deserting their previous combinations in the same time interval, so that neither the number of flowers occupied nor the number of bees on the wing will change any more as time goes on. Of course, it will not always be the same flowers that are occupied and the same bees will not always remain on the wing, but the total numbers of each will have settled down to constant values. And further, the total number of flowers occupied will depend on the total number of bees present.

All analogies are imperfect and this is true of the present

one no less than of others. In the actual solution of hemoglobin we imagine not only the oxygen particles but also the hemoglobin particles with which they combine to be in constant rapid movement, whereas in the garden the flowers which we have taken to represent the hemoglobin particles remain at rest. And then we have had to suppose that the total number of bees in the garden has remained constant, that during the period of observation none has left and no new ones have entered: we have had to suppose that the bees we have been interested in have been cut off from the outside world. Such a condition is not likely to arise under ordinary circumstances in nature, but it represents the way in which our oxygen and hemoglobin are confined to the solution in which they find themselves. In the case of the chemical system we can say exactly what has happened at any moment by carrying out an analysis of the solution and determining the amount of each substance present, but an analysis is nothing more than a kind of counting of particles and so is exactly analogous to the counting of the number of flowers occupied by bees. Of course the rates of movement and of combination of particles such as those of hemoglobin and oxygen are infinitely more rapid than the flight of bees from flower to flower, but apart from this and the other details mentioned our analogy does give a fairly accurate kind of slow motion picture of what we believe to take place, not merely in a solution in which oxygen and hemoglobin are present together, but in any system in which a chemical reaction is occurring.

As we have said, the combination of hemoglobin with oxygen is a process that goes forward with amazing rapidity under quite ordinary conditions, and provided there is an abundant supply of oxygen the whole of the hemoglobin in a solution may be converted into oxyhemoglobin in a few thousandths of a second. But, rapid as the reaction is, two

English workers, Hartridge and Roughton, have succeeded in following it by a method that is so ingenious and so fraught with possibilities of further development that we must devote a few words to it. These two workers took a weak solution of hemoglobin prepared from blood and also a solution of oxygen in water. They squirted these two solutions at each other through fine jets in a mixing chamber so designed that the turbulent currents set up in the liquid were sufficiently violent to mix the solutions completely before the chemical reaction between the hemoglobin and the oxygen had had time to go very far. From this special mixing chamber the mixed liquid was allowed to flow rapidly along a fairly wide horizontal glass tube, and as it passed along this tube the hemoglobin and the oxygen combined with each other.

The liquid near the entrance to the tube was, of course, purple in colour as its hemoglobin was mostly not combined with oxygen; as it flowed along the tube the combination took place and the colour progressively changed from purple to the scarlet of oxyhemoglobin. By means of an optical instrument that told them just how much purple and how much red there was in any particular mixture of these colours, the investigators could determine the exact shade of the colour of the solution and therefore the proportion of free hemoglobin and of oxyhemoglobin at any point along the tube; and they had plenty of time for such an observation, for, although the particular portion of the liquid that they were looking at at any one instant was at once swept on by the rapid stream of the fluid, it was being continuously replaced by other portions of the fluid that had been submitted to exactly the same treatment and so contained exactly the same proportions of the reacting substances. The distribution of colour along the tube, therefore, remained constant although the fluid itself was in rapid movement. The rate at which the fluid was flow-

ing along the tube was very carefully measured so that it was easy to calculate the length of time that elapsed between the moment at which the fluids were mixed and the instant at which they arrived at the point of the tube at which the observation was being made. In this way it was possible to know just how much hemoglobin had combined with oxygen in this calculated interval of time; and by shifting the observation instrument to other points further along the tube it was possible to determine how much combination took place in succeeding intervals, until towards the outflow end of the tube the combination was practically complete. In the actual experiments, let us repeat, the whole process was over in something like a fiftieth of a second, but by forcing the fluids along under pressure it was possible to get them through the tube within this short time. We of course cannot describe in detail here all the investigations that these workers carried out with this ingenious machine; the work is, in fact, still in progress, but the most important result that has appeared so far is that the combination of oxygen and hemoglobin goes on at just such a rate as would be expected if this process were one of simple chemical union, so that we have now no doubt at all that it is.

We must now retrace our steps a little in order to pick up again the main thread of our argument. Let us see first exactly where we stand. We have found that when hemoglobin is brought into contact with a high concentration of oxygen the two substances unite chemically and a new substance—oxyhemoglobin—is produced. This is what happens in the lungs. When this oxyhemoglobin finds itself in a place where the concentration of oxygen is low it breaks up, again chemically, and forms hemoglobin and oxygen once more. This is what happens to the oxyhemoglobin that is present in the blood streaming through an active organ. And the actual amounts of hemoglobin and oxyhemoglobin present

when a solution is brought into equilibrium with a given concentration of oxygen are determined by the relative rates at which the combination and the breakdown occur. But so far we have been saying what would happen to a solution of hemoglobin in *plain water* when it was treated in this fashion. Are we sure that the hemoglobin present in the blood corpuscles behaves in exactly the same way? When we obtain the answer to this question by going through all our experiments with blood instead of a solution of hemoglobin (of course we have to add substances that prevent the blood from clotting in our apparatus, but there is no difficulty about that); and when then we compare the behaviour of blood with that of a plain solution of hemoglobin, we find that in general their main properties with respect to oxygen are the same. The blood takes up oxygen when this gas is present in high concentrations and gives it up again when the concentration of oxygen is reduced, and the total amount of oxygen that a given amount of hemoglobin will take up is the same whether that hemoglobin is present in blood or in plain water.

But a very, very important difference of detail between the two cases appears when the already saturated liquids are taken from a high concentration of oxygen to a low one, for then it is found that the blood gives up much more of its oxygen than the plain hemoglobin solution does. Evidently there are factors in the blood that increase the rate of the breakdown of oxyhemoglobin so that, as it were, the oxygen cannot be so firmly held when the concentration of oxygen is low. Now it will at once be evident that, no matter what the particular factors are that are responsible for this effect, its actual occurrence makes the blood a much more efficient carrier of oxygen than it otherwise would be. For while physiologically it does not seem to be so difficult to ensure the almost complete saturation of the blood with

oxygen as it courses through the lungs under ordinary circumstances, the rapid unloading of the oxygen from the blood as it courses through the active organs where the oxygen is required, does seem to need special mechanisms. It is just like the case of the transport of ordinary goods by railroad: not only is it necessary to ensure the rapid and efficient loading of the goods on to the trucks; if the transport is to be as rapid as possible, it is just as essential to unload the trucks quickly and to send them back at once for more.

So far as the blood is concerned we know what are the most important factors that assist in this rapid unloading of the oxygen. One of these is the circumstance that not only do the blood corpuscles contain hemoglobin and water, but, dissolved in that water at the same time, there are mineral salts. By adding such mineral salts as are found in blood to solutions of hemoglobin in water we can imitate this action and cause the hemoglobin to part with oxygen easily at low oxygen concentrations just as it does in the body. Another factor producing a similar result is the presence of acids in the blood. This is a factor of considerable importance, for, as we have seen, at least two acids are produced in the tissues during their normal working, carbonic acid and lactic acid. Now the significance of this effect of acids is that it will be exerted just where it is most needed, for where a tissue is most active most oxygen will be required, but it is just here also that most acid will be produced during activity and that the oxygen will therefore be most easily liberated—a most remarkably appropriate arrangement. Lastly, there is the circumstance that in ourselves and the higher species of the animal creation the blood runs warm, and this warmth tends to loosen the bond between oxygen and hemoglobin and so to help in the unloading of the oxygen. Taking them all in all it has been calculated that these three factors working

together make the blood about one hundred times as efficient in the carriage of oxygen as a solution of hemoglobin in cold water would be. Even as it is, it is hard enough for us to be really satisfactorily active, so that the lethargy into which we would sink if our blood had not this surprising efficiency in the transport of oxygen can well be imagined.

But this is not altogether a matter for imagination for unfortunately the effects of interference with the normal transport of oxygen by the blood are sometimes disastrously illustrated in everyday life. This arises from the circumstance that oxygen is not the only gas with which hemoglobin will combine. There is a poisonous gas—*carbon monoxide*—that has 300 times as great an affinity for hemoglobin as oxygen has; so that if this gas and oxygen were competing, as it were, for a given amount of hemoglobin, the carbon monoxide would get practically all of it. And once carbon monoxide has combined with hemoglobin, the product of their union—*carbon monoxide-hemoglobin*—is very difficult to break up again. Carbon monoxide is so poisonous, therefore, because it puts the hemoglobin of the blood out of action, and so robs the body of its needful oxygen. Now all this is important because it is quite possible that a person might come into contact with this poisonous carbon monoxide under quite ordinary circumstances. For one thing, carbon monoxide is an abundant constituent of ordinary coal gas, so that anyone who shares a room with a leaky gas pipe will be continuously inhaling a certain quantity of it. Then again, carbon monoxide is formed whenever carbonaceous fuel is burned with a limited supply of air, as, for example, in an automobile cylinder. It is therefore abundant in exhaust gases. We can now see the reason why a man is liable to be poisoned—perhaps fatally—if he runs an automobile engine in a closed garage. The carbon monoxide from the engine combines with

the hemoglobin of his blood and so prevents it from taking up and transporting oxygen, for the hemoglobin cannot combine with both gases at the same time. It is very probable that the less serious but depressing effects of being in a busy street are in large measure due to the carbon monoxide that the automobiles send out into the air.

We might just pause for a moment to contrast this poisonous product of partial combustion, carbon *mon*oxide, which contains *one* proportion of oxygen to one of carbon, with the product of complete combustion, carbon *di*oxide, which contains two proportions of oxygen to one of carbon, and is a much less dangerous substance, being produced, as we have seen, in large quantities as the end product of the combustion occurring in the body.

The treatment for a man who has been "gassed" by an automobile is to force as much fresh air as possible in and out of his lungs, in order that the carbon monoxide may be expelled from its combination with the hemoglobin and replaced by oxygen.

We have now said a great deal about what might be called the use of hemoglobin in the body, but so far never a word as to what manner of stuff it is. That we could go so far without describing the chemical make-up of the substance is due to the circumstance that hemoglobin is used over and over again for the function of oxygen transport and, unlike many other materials, its use does not involve its destruction. But in order to understand the steps whereby the body first makes its store of hemoglobin and to be able to follow the fate of such portions of the substance as, after a long period of the kind of usefulness we have described, do ultimately go to pieces, we do require a knowledge of its chemical structure. We find out the chemical constitution of hemoglobin by the same general method that we adopt in investigating

other complicated substances, that is, we make a careful study of the simpler products obtained by breaking it up. When we break up hemoglobin by adding to it just the right amount, but not too much, of a strong acid we obtain from it two products. One of these on further examination turns out to be a protein, called *globin,* the other is not a protein but, nevertheless a fairly complex compound, called *hem.* When we express this result schematically its simplicity at once appears:

$$\text{hemoglobin} \longrightarrow \text{hem} + \text{globin}$$

Thus we discover, if indeed we had not guessed it already, that hemoglobin is a really complicated substance, for it is a compound of two substances each of which is itself complicated enough. Of these two constituents hem is certainly the more interesting, for when it is treated with a lot of really strong acid it is itself further broken up and one of the products is no less a material than iron. Hem is a compound of iron. Now in describing the carriage of oxygen by hemoglobin we pointed out by way of contrast what an unsuitable material iron itself would be for the transport of oxygen under the conditions that exist in the body. But we were then of course speaking of plain metallic iron itself. Let the iron be combined as a constituent of hem, and let this be united with globin to form hemoglobin, and we have a material about whose oxygen-carrying powers we can be really enthusiastic —as indeed we have been. With what then is the iron combined in order to form hem? This is a question that is not so easy to answer, not because the answer is not well known, but because it is not easy to explain in simple language. The iron in hem is combined with one of a group of substances known as the *porphyrins* and this particular porphyrin is known as the blood porphyrin—*hematoporphyrin.* "But,"

the reader will protest, "what is the use of telling us that when we do not know what a porphyrin is?" And that is where the difficulty lies. The name porphyrin itself is derived from the Greek πορφύρεος meaning "purple," and expresses the fact that this porphyrin obtainable from blood has a rich purple colour—as anyone can see for himself who will prick his finger and allow a drop or two of blood to fall into a little strong sulphuric acid. The strong acid at first splits apart the hem and the globin and then takes the iron from the hem leaving hematoporphyrin, thus carrying out in one step, so to speak, the decompositions that we have described in stages.

It is interesting that the same decomposition occurs normally in the body. It is not easy to say exactly what is the average life of a red blood corpuscle, but we do know that it is a limited one, and that sooner or later these useful cells become, as it were, worn out and replaced by new ones. When this happens the same hemoglobin is not used again; it also is broken down. The new red blood cell starts with a load of freshly made hemoglobin, while the old pigment is broken down in the same way in the body as it would be in a test-tube of strong acid. Its globin is separated from the hem and the hem itself is split up into iron and porphyrin. The iron becomes stored in the liver for subsequent use while the porphyrin is used, also by the liver, as a starting point in the manufacture of those greenish-yellow pigments that give so characteristic a colour to the bile. Everyone who has seen a case of jaundice (in which condition the outflow of bile from the liver into the intestine is obstructed so that the bile finds its way into the blood and so gets carried all over the body) will know the colour we mean.

But we must return to the porphyrins, difficult though they are to describe. As the result of a large amount of careful chemical investigation it has been found that hematopor-

phyrin obtained from hemoglobin in the way we have described is a compound containing a lot of carbon and hydrogen, oxygen and nitrogen, and that these materials are arranged in angular five corner "rings" so that the formula by which the chemist describes the chemical structure of this substance comes to look something like a patch of crazy pavement in a garden path. But, as we have meant to imply by using the word in the plural, there is not merely one but a whole group of porphyrins all possessing the same kind of chemical skeleton and differing between themselves merely in the smaller details of their chemical structure. These porphyrins are usually found as constituents of pigments in both the animal and vegetable kingdoms, and as such have a very wide distribution. Not all of them are purple. They are found not only in the colouring matter of the blood of many animals but also in the gay plumage of tropical birds and in the patches of bright colour on the shells of eggs. And what is of special significance is that porphyrins form essential constituents of the green colouring material of leaves, and so contribute in a very special way to the outstanding feature of our terrestrial landscapes. Of this more later.

We have just mentioned the way in which hemoglobin is decomposed in the body but we have said nothing about the reverse process by which it is built up. There seems little doubt that the body can manufacture from simpler materials all the porphyrin it requires, can combine this with iron to form hem and this in turn with globin (which it can build up as easily as other proteins) to form hemoglobin. It is evident that for this process of synthesis to go forward an adequate supply of iron is indispensable and that this can come only from the food. Certainly, as we have seen, the body works very economically with regard to iron, which it stores and uses over and over again. But there is always some waste that has to be made good from the iron that forms a constituent of

many foods. Meat supplies us with iron because it contains hemoglobin; green vegetables are also valuable sources of iron, and dandelion leaves are said to contain ten times as much of it as any other green stuff. Milk contains practically no iron, and this is an important fact in connection with the feeding of infants, for growth in the size of the body involves a corresponding increase in the total amount of blood, and this blood cannot be supplied with the correct amount of hemoglobin unless there is available the necessary amount of iron for its manufacture. A new-born infant starts life with a good stock of iron that it has received from its mother and stowed away in its liver. This stored iron is sufficient to supply all it needs for the formation of the hemoglobin that it will normally manufacture during the first six months of its life, so that it matters nothing that the milk it receives contains practically none of the metal. But after it is six months old it needs to begin to take in iron from the outside and if it does not do so—if, for example, it is kept too long on a milk diet and is not weaned at the proper time (as may happen if its mother believes in the long since disproven superstition that as long as she suckles one child she cannot conceive another)—it will certainly become anemic—that is, bloodless—because it is not getting the iron it needs for the formation of good rich red blood.

But we are wandering far from our main topic. Let us leave the questions of the chemical constitution and synthesis of hemoglobin and refer once again to its uses in the organism. Oxygen is not the only gas that is carried by the blood in the body. At the same time as it is unloading its oxygen to an active organ the blood is taking up the carbon dioxide produced during the combustion that takes place in the organ and it is in the blood that the carbon dioxide is transported to the lungs, there to pass out of the body in the expired breath. Now hemoglobin plays just as important a part in

the transport of carbon dioxide in the blood as in the transport of oxygen. It is not that the hemoglobin unites directly with carbonic acid as it does with oxygen, but rather it holds loosely combined within its structure a store of alkali which combines with, and at the same time neutralises, the acid gas as it is taken up. Then when the blood arrives at the lungs the hemoglobin takes back the alkali and liberates the carbon dioxide so that it is free to be breathed out together with the truths, the lies and the calumnies that in their turn issue from the mouth of man. And further it has been found that oxyhemoglobin has a more powerful affinity for the alkali than has hemoglobin not combined with oxygen, which means that as the blood takes up oxygen in the lungs and oxyhemoglobin is formed, the carbonic acid is all the more completely dissociated from the alkali with which it is combined and so is all the more efficiently expelled. When we were speaking of the transport of oxygen we found that the carbonic acid helped the unloading of oxygen from the blood to the tissues, and now we find that oxygen helps the unloading of the carbonic acid from the blood to the air in the lungs. This intimate relation between the properties of hemoglobin and the transport of carbonic acid in the body has been established only fairly recently, for unlike its combination with oxygen this "lending" of alkali on the part of hemoglobin for the transport of carbonic acid takes place very modestly and is not advertised by any such striking change of colour as accompanies the formation of oxyhemoglobin. It is only natural, therefore, that it should have been longer in attracting attention than was the fundamental process in oxygen transport.

Were we to go into details with regard to the part played by hemoglobin in the transport of carbon dioxide and in the maintenance of that slight alkalinity of the blood that is so important for the proper functioning of the organs of

the body, we could fill a whole chapter that would be at least as lengthy as the present one has been. And it would not be easy reading. But that is obviously impossible now. Other subjects, other materials demand our attention. We cannot give more time to the study of this one substance. But let us not leave it without expressing the hope that we have in some measure made it clear why hemoglobin has come to be called the most interesting substance in the world—interesting because there is no other that shares its unique properties, interesting on account of the use to which these properties are put in the maintenance of animal life, but interesting also for the philosophical speculations to which it gives rise as to how so useful a substance comes to occupy just that place in the scheme of nature where its capabilities are so efficiently employed.

XII

HEALTH AND VITAMINS

To most people in these days the word *vitamin* is not a new one. We meet it so often in the daily press, in articles in our home magazines and in the advertisements of food products, that most of us know it refers to something that is not merely good but essential to eat. But in spite of this widespread familiarity the word itself is not so very many years old—in fact, practically all of our modern scientific knowledge of vitamins has been gathered in the last couple of decades. During that time it has come to be realised that even if we provide a man or animal with a diet yielding enough calories to supply his energy needs and containing enough good protein for the maintenance of his tissues, and sufficient quantities of the mineral salts he requires, he will not remain in good health unless his food also contains small but adequate amounts of these much talked-of vitamins. And if the individual in question is still at the growing stage the development of his bodily structure will be much impeded or even completely prevented if he does not get all the vitamins he needs.

Vitamins, then, are substances that we must eat in small amounts if we are to grow properly and to keep well. Any deficiency in their amount leads to the onset of distressing discords known as *deficiency diseases*. Of these we mentioned one—*rickets*—in our introductory chapter, but this is far from being the only one of these deficiency diseases with whose causes and prevention we shall have to deal.

Sore eyes, stunted growth, scurvy, and degeneration of the nerves are possible results of the absence of one or other of the vitamin substances from the food, and it is our object in this chapter to give an account of the vtiamins that prevent these disorders, and to indicate the foods in which they are contained in greatest abundance. In doing this we shall be describing one way in which the biochemist takes part in the ceaseless fight that humanity has to wage against disease. This is a topic we shall deal with more specifically in a later chapter; but there we shall describe cases in which the biochemist can furnish materials for the cure or relief of diseases that have occurred through circumstances that are at present in great measure beyond our control, while in the present chapter we shall be dealing with something which is proverbially better—namely, the prevention of diseases that need never occur at all and that will be completely abolished so soon as we can ensure to every individual a diet that is in accordance with what modern biochemical researches have shown the needs of the body to be.

It might occur to the reader to ask at this point "How is it, seeing that such serious maladies arise as the result of eating food that does not contain enough vitamins, that even our remote ancestors managed to grow properly and keep well?" One might even wonder how we ourselves have succeeded in attaining a reasonably good standard of physical fitness although our own parents knew nothing of vitamins. The answer is that under natural conditions mankind has been eating vitamins for ages, but it is only recently that as a result of scientific study of diet these important substances have been recognised and called by that name.

One reason why vitamins have come into such prominence lately is that we have begun to depart considerably from the dietetic habits of our more primitive forefathers. They ate mostly food fresh from the soil on which they them-

selves had grown it or from the wilds where they had hunted it—and such food is teeming with vitamins. But in these days so many of us live in towns and do very little of the raising or capture of food for ourselves. This is of necessity left to others who inhabit parts of the country that are particularly suited by soil or climate for the purpose. The food they produce has then to be kept for considerable periods of time and in many cases must be transported over very large distances, so that when it arrives at the store whence we obtain it, it is anything but fresh. But vitamins —and this is the important point to bear in mind—are substances that do not last long and do not carry well. A food may contain abundance of some particular vitamin when fresh, but by the time it has been submitted to the processes of preservation and storage incidental to its transport to a town population, its vitamins may have become completely destroyed, although its proteins, fats and carbohydrates may still retain their nutritive values practically unchanged. The food would therefore be quite suitable for supplying energy to the body and for maintaining its tissues but it would not contain the vitamins necessary for continued health.

The vitamins are particularly sensitive to heat, so that any process that requires the food to be heated to a relatively high temperature for any length of time will almost certainly destroy its vitamins. This will be the case, of course, with ordinary cooking, but will be very specially true of the process of canning in which the food, once it has been placed in the can, must be heated to a sufficiently high temperature and for a sufficient length of time to kill all the bacteria that are present in it, for these would otherwise set up the changes we know as putrefaction and decay. Thus it comes about that as we rely more and more on preserved and canned foods, and as the modern housewife becomes

more and more expert in wielding the can opener, the problem of the supply of our needed vitamins becomes an increasingly serious one for us. Or rather, it would become serious were it not for the large amount of scientific study that has been and is still being devoted to it. And here we might mention that one of the factors that is helping in great measure to solve this problem of vitamin supply is the widespread use of electric refrigeration by means of which even in the smallest of apartments fresh foods may be stored without loss of the vitamins they and they alone contain.

So far, then, we have explained that vitamins are substances present in fresh but not in most preserved foods and that they must be eaten in sufficient quantities if normal health is to be maintained and the deficiency diseases are to be avoided. By this time, however, the reader will probably be impatient to pass on from this general statement to consider just how many vitamins have been recognised up to the present, in what particular foods they occur most abundantly; and which particular malady each is capable of preventing. It is of course only such detailed information that can be of use to us in making out a diet that will supply the vitamin requirements of an individual, and indeed it was not until this detailed information had been collected that it became possible to make the general statements about vitamins with which we have introduced this chapter. Roughly speaking, the known vitamins are about as numerous as the deficiency diseases we have mentioned, and we must consider them all in turn. Perhaps it will be best to deal with them in the historical order in which they were discovered.

The story begins way back in 1897 when a Dutch physician, named Eijkman, was medical officer to a number of prisons and similar institutions in Java. At that time one of the chief problems a medical officer in the Far East had to grap-

ple with was that presented by the disease known as *beri-beri*. This is a very serious affection in which the nerves of the patient go all wrong. They break up and degenerate so that they become quite incapable of carrying their normal messages or impulses. The sufferer therefore loses all control of the muscles of his trunk and limbs, and ultimately collapses in a condition of complete paralysis. From such a serious condition the patient rarely recovers as the disease usually affects the heart, and death through heart failure occurs. It remains to mention that it is practically only the natives of Eastern countries where the chief article of diet is rice who are liable to suffer from this beri-beri. Now in one of the prisons of which Eijkman had control a number of hens were kept about the yard, and for a long time the birds were allowed to go round and pick up such miscellaneous scraps of food as they could find. On this diet they remained perfectly healthy. And then suddenly, for no apparent reason, one day they collapsed in a paralysed condition exactly like that of a man suffering from beri-beri; in fact, it was obvious that the birds had in some way "caught" the disease.

Eijkman at once realised that if he could find out exactly what had led to the onset of the disease in the birds he might get a very important clue to the factors that produced it among his prisoners. On inquiry he found that during the period when the birds fell ill their diet had without his knowledge been changed. Instead of allowing them to wander about and pick up a very mixed diet containing all sorts of materials from the refuse heaps of the institution, the servants had taken to feeding them on the remains of the rice that had been served to the human inmates of the establishment. Now this rice, as it happened, had been "polished," as it is said, that is, it had been milled by means of modern steel rollers which had removed much more completely than the natives' primitive stone mills had previously

done, not only the husk corresponding to the bran of wheat but also the germ and the outer layers of the actual rice grains. Apparently the natives, like ourselves, prefer to eat rice that has been treated in this way just as many of us prefer to eat white bread. The effect of the polished rice on the birds made it seem likely that the change of diet had been responsible for the disease, and this was actually proved to be the case when the birds very quickly regained their normal health as soon as their original mixed diet was restored to them. Eijkman showed also that in just the same way it was the eating of too much polished rice that produced the disease in man. On comparing the frequency of the disease in a number of prisons he found that the greater the proportion of polished rice eaten by the inmates, the more cases of beri-beri they reported. At first Eijkman thought that the fault of the polished rice diet lay in its containing too great a proportion of starch, and that the bran of the rice contained something that was necessary for avoiding the harmful effects of so great an excess of carbohydrate. In fact this was the point to which his ideas on the matter had developed when he was recalled from the East to occupy a professorship in his home country, Holland. The subject was further studied by his successor, Grijns, who realised that beri-beri is brought on, not because the polished rice diet contains too much starch, but because it lacks some particular substance that is necessary for the normal health of the nerves. This substance is contained in the bran of the rice and is removed when this is milled or polished away, so that it comes about that an individual who eats nothing but rice—and this is true of most of the poorer natives—will get none of this needed substance. A European or American living in the East does not suffer from beri-beri because his diet is so mixed that he obtains this necessary substance from other sources. The next step in the investigation was taken by a Polish chemist named Casimir Funk,

who argued that if the bran of rice contains the substance necessary for the prevention of beri-beri, it should be possible in some way to extract this substance from the bran and to prepare it in a form in which it could be administered to an individual and so to cure him of his disease. The old adage that where there's a will there's a way is as true of scientific work as of most human effort, even though sometimes the way may be hard to find and difficult to follow when found. In the case of Funk's experiments the way consisted in extracting the bran with alcohol of a suitable strength and recovering the material that had dissolved in the alcohol. When this material was then dissolved in plain water and the solution injected into a bird that had completely collapsed with beri-beri, improvement in the bird's condition was found to be very rapid. It was only a matter of minutes before the bird was obviously better and only a few hours before it was on its feet again and once more enjoying the pleasures of avian life. Evidently Funk had in this way isolated a material essential for normal health, and indeed for the continuance of life itself. He called it "vitamine"—a word by which he intended to express the idea that it was necessary for life (Latin *vis, vitis*) and that it belonged to the group of substances the chemist calls "amines." Now amines are alkaline basic substances that contain nitrogen as one constituent, and further investigation showed that Funk's vitamine did not really belong to this class. So, as chemists have got into the habit of reserving names ending in "ine" for substances that are really amines, we now omit the last "e" from the name of the material that Funk isolated and call it *vitamin.*

But even before Funk had succeeded in extracting his "vitamine" from rice polishings, Hopkins, in England, had become convinced that there was some special kind of virtue in fresh food that is lacking in prepared or preserved food, and he decided to put the matter to the test in a very simple

and straightforward way. He took two batches of young rats as nearly as possible alike. One of these batches was fed on a diet composed of carefully purified casein (the chief protein of milk) starch, cane sugar, lard and mineral salts. It will be seen that this mixture contains proteins, fats, carbohydrates and mineral materials, so that from all that we have said in earlier chapters about diet it would be expected to constitute a diet on which the rats would thrive and grow. But although the animals ate it greedily they soon became sickly and under-developed and ceased to increase in weight —that is, to grow. The rats of the second batch received as the main part of their food exactly this same mixture but in addition they were given two cubic centimeters—a small spoonful—of fresh milk every day. This small addition to the food was found to make all the difference and the animals of batch number 2 grew as only young rats know how. Then, in order to be quite sure that he had not by chance chosen more healthy rats for batch 2 than for batch 1, Hopkins began to give the milk to the animals that had previously not received it, and to give the thriving animals of batch 2 only the artificial food mixture. It was now found that the sickly animals of the first batch began to show a normal increase of weight from day to day and soon made up for the time they had lost by being on the inadequate food, while the well-grown animals that were now deprived of their milk soon ceased to continue their growth and later began to lose weight, that is, to waste away.

This experiment is such an important and fundamental one in the science of dietetics that we shall emphasise it by presenting the reader in the following figure (5) with a copy of the diagram by means of which Hopkins expressed his results. It is quite easy to understand. The numbers along the bottom horizontal line of the diagram represent the successive days during which the experiment lasted, and the numbers up the

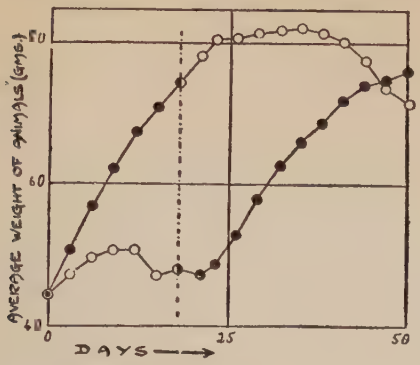


FIGURE 5. The influence of the vitamins in fresh milk on the growth of rats. The animals whose weights are represented by white circles received only the basal diet: the animals whose weights are represented by black circles received a little milk in addition.

(Courtesy of Messrs. Heffer and Sons.)

vertical side represent the average weight of a rat of one or the other batch. The results of the experiment are recorded on the diagram by placing a dot over the number of the day on which a particular weighing was made and level with the number on the vertical scale corresponding to the rat's actual weight on that day, in exactly the same way as a nurse enters the temperature of a patient on a temperature chart, or a recording barometer makes a record of the variations of atmospheric pressure. By joining all these dots we then get a curve that gives us a clear picture of the way in which the weight of the rats varied during the experiment. Of course in this case we have two such curves—one for each batch of rats. It remains merely to add that on this diagram black dots are used to express the weights of rats receiving the fresh milk ration and white circles to represent the weights of the rats receiving only the artificial food mixture, with, of course, as much water as they would drink. A mere glance at the diagram is sufficient to convince the reader that

it is only when the rats are receiving the fresh milk that they increase in weight or grow. And yet the amount of milk they receive is much too small to yield all the material they lay down in their new tissues. It is evident from this that the fresh milk must contain some substance or substances that the rat must have if it is to be able to utilise the materials supplied in the main bulk of its food for that production of new living matter which the process of growth involves. These growth-promoting substances thus recognised by Hopkins were first called by him "accessory factors of the diet" because they are accessory or additional to the requirements of proteins, fats and carbohydrates recognised at that time as the essential components of food.

These striking results of Hopkins' experiments stimulated a great deal of interest in the subject of these accessory food factors, especially in America where it has been studied by such investigators as Osborne and Mendel and McCollum and Davis. We cannot go into the details of all the work carried out by these and other workers. Suffice it to say that, as a result, it gradually became recognised that, in order that normal growth of the body shall occur, not merely one but *two* such accessory factors must be supplied in small quantities in the food. One of these was found to be present in such animal fats as butter and cod liver oil, but not in lard or olive oil. This factor was named *fat-soluble A*. The other factor was found to be present in the watery parts of fresh food and was therefore called *water-soluble B*. Very soon it was realised that this water-soluble B was a substance very similar to if not identical with the "vitamine" that Funk had extracted from rice bran and so the name *vitamin B* began to be applied to it. It was then only natural that the fat-soluble accessory factor came to be called *vitamin A*. Nowadays we use the name vitamin for all of these and the other factors that have since been recognised. As we have said, vitamin A

occurs in butter fat which is simply the fat of milk, so that it will be present in fresh milk itself. Vitamin B also occurs in milk; it remains behind in the watery part or whey after the fat has been removed and clings obstinately to the milk sugar when this is extracted from the milk. Vitamin B is also present in large amounts in yeast. We can now easily understand how it was that the rats in Hopkins' experiment fared so badly when they received only the artificial food mixture. For as fat he had given them lard (which does not contain vitamin A) and as carbohydrates he had given them starch and *cane* sugar (neither of which is likely to be contaminated with vitamin B as milk sugar would be) so that the rats were robbed at the same time of two vitamins necessary for their proper growth.

A little while ago we said that the story of vitamins begins with Eijkman's work on beri-beri in 1897. But when we look back from the vantage ground of our present knowledge we can see many, many instances where men have in much earlier times been stricken by diseases that we now know to be caused by lack of vitamins, and have tried to fight them by the empirical means and knowledge then at their command. This is particularly well illustrated when we look into the records of *scurvy,* the disease which from time immemorial has made its ravages among the crews of ships, the members of exploring parties, and other groups of men whose occupations or adventures have carried them into places where for a long time they have been cut off from a supply of fresh food. This scurvy is a really serious ailment: its chief and most distressing symptom is extensive bleeding which takes place from the gums and round the joints. The result is that the sufferer becomes quite incapacitated and in olden times was often left to die. Two hundred years ago scurvy was referred to as "the most loathsome disease in nature" on account of the circumstance that there appeared to be no

drug in the apothecary's medicine chest that could alleviate its pain. But even in those days it was clearly realised that the disease did not occur in persons who could get a sufficient amount of fresh fruit and green vegetables, and that the eating of these foods would cure an already afflicted patient in a day or two if the illness had not got too great a hold on him. As more and more experience of this kind accumulated everyone became convinced that scurvy was due not to a form of poisoning by some harmful constituent of preserved foods but to the lack of some scurvy-preventing substance that is present in greatest abundance in fresh vegetable foods. By "fresh" we mean in this connection not merely sound, but also not cooked or dried. It has been known for more than a century that the lemon is one of the best fruits for the prevention of scurvy and that its juice retains its efficacy even after it has been stored for a considerable time. For this reason it became the custom for lemon juice to be served regularly to crews of ships and to be carried by exploring parties. But unfortunately faith in the value of this measure was shaken for a time when *lime* juice began to take the place of lemon juice for this purpose. Several cases occurred in which expeditions well supplied with lime juice were no more successful in preventing scurvy than others that carried none of it, so that the use of fruit juices in general fell into disrepute. Because the two fruits are so much alike in most respects, it never occurred to anyone to inquire whether there might not be a significant difference in composition between the juice of the West Indian lime and that of the Mediterranean lemon. For one thing, they seemed to be about equally acid, and it was upon this acidity that their beneficial effects were supposed to depend. Now, however, as the result of recent investigations, we know that as a matter of fact there is a very considerable difference between the two fruits, and that while the lemon really does contain an

abundance of the scurvy-preventing substance the lime is almost devoid of it.

Apart from these more or less unintentional experiments carried out on the members of ships' crews and exploring parties the first really scientific laboratory investigation of this important nutritional factor was made by Holst in 1907. He worked in what was then known as Christiania—the modern Oslo. (Notice how amazingly international scientific work is!) In order to study the importance of fresh vegetable foods for the prevention of scurvy he decided to withhold from his laboratory guinea pigs their usual ration of cabbage leaves and other green stuff. As a result the animals soon developed unmistakable symptoms of scurvy, with bleeding at the joints and other effects, and in a few weeks were dead. But no such calamity occurred when they were given an ounce of fresh raw cabbage leaves a day, or a similar quantity of other fresh vegetable food. The guinea pigs that did develop scurvy were fed on oats, barley, and other grain as well as wheaten and rye bread, so that we can at once see that the anti-scurvy substance, whatever it is, is not present in these dry seeds and cereal foods. In this respect it shows a marked contrast to the anti-beri-beri vitamin B which, as we have seen, is present in the dry cereals, such as rice, provided no part of the seed is removed by milling. But of course there is one obvious way in which we can convert a dry seed into a fresh green vegetable, and that is to allow germination to take place. And Holst proved that the seedling plants obtained in this way are just as good for the prevention of scurvy as other fresh vegetable products are. It has therefore been proposed that in future when an expedition is to be sent into a region where fresh vegetables are scarce it shall carry with it a supply of dry seeds (which are so easy to transport and store) and shall obtain its supplies of the anti-scurvy substance by causing these seeds to

germinate as required. It is not alone cereal grains that will serve for this purpose: such legumes as peas and beans may be used just as well. We thus see that the manufacture of this anti-scurvy substance is one of the many complicated chemical changes that take place in a seed during its germination.

Now by this time the reader will have guessed that this anti-scurvy substance is nothing less than another vitamin, and as the letters A and B are reserved for the ones we have already described, this latest one is now called *vitamin C*. We thus have mentioned three vitamins so far—A, B, and C. Actually these letters are nothing more than convenient labels for these substances. We do not know nearly enough about any one of them to be able to give even the general outlines of its chemical formula but this much is certain, that they are all complicated substances, so that when we know them the formulas will undoubtedly be much more difficult than this simple A, B, C.

But although their formulas may be uncertain, there is no doubt of the importance of vitamins in the prevention of disease. Let us repeat this part of the story in order that the main facts may remain clearly in mind. A is the vitamin found in fats: so far we have said only that it is necessary for growth. B is a water-soluble vitamin necessary for general growth and in particular for the healthy maintenance of the nerves in normal condition. It is found in dry seeds and in yeast. Lastly, C, which is also a water-soluble vitamin, is necessary for the prevention of scurvy. It is not present in dry seeds until they have germinated, but is abundant in fresh vegetables and fruits. This is a very brief summary of what was known about vitamins at the time of the outbreak of the war, and we must now go on to consider some of the more important of the newer results that have

been obtained from the enormous amount of work devoted to the subject since that time.

Even the war did not delay the study of vitamins as much as it hindered the development of many other aspects of human culture, for the governments of all the great nations were faced with the problem of feeding their populations at a time when, owing to complete failure on the part of those to whom the maintenance of the world's peace had been entrusted, the food supply of millions of human beings was in danger of running short. Under these conditions it was necessary to ensure that not only proteins, fats and carbohydrates but also vitamins were distributed as economically and as scientifically as existing knowledge and available supplies would permit. At that time every well-proven item of knowledge was of value in conserving the national resources, and in rendering less acute the calamities to which the politicians had brought us all.

But to consider the recent knowledge that has been gained about vitamins. We have seen that the fat-soluble vitamin A must be present in the food of baby animals—including human babies—if they are to grow in a satisfactory way. But a mere general failure to grow is by no means the only disturbance of health and normal development that a young child may show. There is, all too prevalent among the children reared in the poorer districts of our large towns, a disease in which it is specially the bones that are not properly developed. The limb bones are weak and the child is bow-legged, the ribs are not strong enough to give the necessary support and the chest becomes hollow, the skull is soft and becomes deformed—the child is, in short, rickety. Its skeleton is affected by *rickets*. Not so long ago this disease was thought to be caused by a special kind of bacterium. But during the last ten years feeding-experiments with puppies have proved that it is produced when the food does not contain

enough fat-soluble vitamin and that it can be promptly cured when fat containing plenty of vitamins—fresh butter will do but cod liver is particularly effective—is added to the diet. There is thus no longer any doubt at all that rickets is a deficiency disease caused by a deficiency of a vitamin in the food. At first it was thought that this vitamin was the same as vitamin A, the fat-soluble vitamin necessary for general growth, but as some plant foods have been found that contain the growth vitamin but are powerless to prevent the onset of rickets, it is now realised that the anti-rickets vitamin must be a separate substance. It is therefore called *vitamin D.*

But this is not the whole of the story about rickets. As we said when introducing the subject, rickets is a disease that is especially prevalent among children brought up in dark, dismal back alleys of large towns. It was only natural therefore that those who were particularly impressed with this fact should ascribe the occurrence of the disease to the lack of sunlight and fresh air, and that they should at first refuse to believe that it is caused by the lack of vitamin D in the diet. After a considerable amount of somewhat heated discussion had taken place between the members of these two opposing schools of thought as to the cause of rickets, it occurred to the investigators in this field to go back to their laboratories and actually try to decide by direct experiment whether light had really any effect on the disease. And when the thing was tried it was found that young rats reared on a rickets-producing diet did not develop the disease if they were freely exposed to light. Then it was further found—to the great surprise of everybody—that it was not necessary to expose the animal itself to light; it was quite sufficient if its food had been "irradiated," as it is said: again no rickets developed. Lastly, it proved to be enough just to flood

the empty animal cages with light before the animals were placed to live in them, but this was soon found to be due, not to an effect of the light on the material of which the cage was made or on the air in the cage, but to some change produced in the sawdust with which the floor was strewn. The rats were seen to eat some of this sawdust and so to obtain the same benefit as those that were fed on the irradiated food. In other words, they were protected against rickets although their diet (apart from the sawdust they ate) was such as to bring on the disease. Now what does this mean? If we expose the young animals (or even their food) to light they do not develop rickets even though we give them no vitamin D: the light can act as a substitute for the vitamin. This suggests that when the animal's body or its food is exposed to light a supply of vitamin is formed in it so that there is no need for the animal to eat the vitamin ready made; and as a matter of fact it was not long before this suggestion was proved to be the true explanation of the effect. What is more, we know also the particular constituent of the food or of the body that produces the vitamin on exposure to light. It is a substance known to the chemists as *ergosterol* and is found in the fatty portion of foods and tissues but is not itself a true fat.

This ergosterol alone has no power of preventing rickets but when it is exposed to light it, or more strictly speaking a small fraction of it, is converted into some other substance that is a very powerful preventive of rickets and is also a very efficient remedy for the disease if this has already become established. So far as we know, it is the anti-rickets vitamin itself that is formed in this way. There seems little doubt that this is what happens in ourselves while we are taking our summer holidays. Apart from the rest and change of occupation that these holidays provide, through the extra exposure to sunlight out of doors, they serve to load us up

with vitamin D which is of value to us even if we may not be so far neglected as to be suffering from rickets.

We thus see that each of the theories as to the origin of rickets is correct as far as it goes, although neither contains the whole truth. For while it is certain that the immediate cause of the disease is a lack of vitamin D it is also true that exposure to light leads to the building up of the vitamin in the body and so reduces the amount that must be supplied in the food. Or—expressing it somewhat differently—we can say that exposure to light will prevent rickets in a growing animal or child even when it is receiving a diet so deficient that the onset of the disease would be inevitable in the dark. So that for a child receiving a given diet the amount of light to which it is exposed in its daily surroundings may be the deciding factor in determining whether or no it will remain in normal health or become rickety.

Before we go further with this topic we ought to pause for a moment to say something about the quality of the light that is required in this connection. Everyone who is interested in photography knows that of all the coloured rays that go to make up ordinary white light it is the violet and ultra-violet rays that exert the most marked effect on plates and films, while the rays of longer wave-length, such as, for example, the red, are so inactive that they can be used to illuminate the dark room in which plates and films can be freely exposed without suffering change. Now the blackening of silver compounds by light, which is the fundamental phenomenon made use of in photography, is but one instance of a chemical change brought about under the influence of light. Many other chemical reactions can be set going when light is allowed to fall on various materials, and in by far the majority of cases it is found that it is the short wave-length light—the violet and ultra-violet rays—that is the most active in inducing the change. The formation of vita-

min D from ergosterol in the body of an animal exposed to light forms no exception; in this case also it is the *ultra-violet* rays that are by far the most effective. It must therefore be understood that when in the preceding paragraphs we have referred to "light" we have meant light containing its full complement of active ultra-violet rays. It is necessary to mention this because the ordinary brightness of a light gives practically no clue to the proportion of ultra-violet rays it contains. At first sight it would seem, for example, that sunlight comes practically unchanged through the panes of our ordinary windows. But physical experiments show that ordinary window glass is practically completely opaque to the ultra-violet rays so that light that has passed through a window will be useless for the production of vitamin D in the body, although its deficiency in active rays will not be apparent to the unaided eye. Of recent years kinds of glass have been invented that are transparent to ultra-violet rays, and attempts are being made to extend the use of such glass as widely as possible, though at the moment it is practically only large institutions, like hospitals, that can afford to buy it. But there is no doubt as to the benefits that would accrue if it were employed in every nursery, school, factory and office, indeed in every building in which men have to spend any considerable fraction of their waking hours. At present all we can do in this connection is to recommend everyone to adopt the habit of getting as much exposure as possible to direct sunshine out of doors.

It is this recognition of the beneficial effect of exposing the body to light that has led to the appearance on the market in recent years of a large number of "sunshine" lamps intended to be used as sources of active rays at times and under circumstances in which sun-bathing would be impracticable. Of the soundness of the principle of using artificial sources of ultra-violet light when our great natural source is

not available there can be no question; nevertheless a considerable amount of caution and expert knowledge are necessary in the use of such apparatus if failure and disappointment, if not positive damage, are to be avoided. In the first place, it is necessary to be certain that the lamp is so constructed that it does really give off the active rays required of it: worthless imitations are in this case so easy to produce. Then it must also be ascertained that the malady against which it is to be used is amenable to light treatment. And lastly, care must be taken in the regulation of the dose of light used. Anyone who has suffered from a severe sunburn will realise that the effects of too much radiation may be not merely uncomfortable but quite definitely harmful to the affected tissues. Usually it is necessary to commence the treatment with quite short exposures and to increase the dose only very gradually until the skin becomes acclimatised. At the same time great care must be taken to protect the eyes against the harmful effects of the light. Taking all these circumstances into account, it will be readily realised that such a powerful agent as ultra-violet light, beneficial as its effects may be when it is suitably applied, must not be used indiscriminately and without proper expert control.

Before we leave this discussion of the beneficial influence of light in leading to a formation of extra supplies of anti-rickets vitamin in the body, there is one more aspect of its importance that we must mention. What we have said about the formation of this vitamin in the bodies of human beings and of rats applies also to the case of our domestic cattle. It has been found, for example, that cows synthesise within themselves much more of the anti-rickets vitamin when they are exposed to sunlight in open pastures during the summer than when they are confined to dark indoor stalls during the winter. This difference of vitamin production shows itself in differences in the vitamin content of the milk

from these cows. The milk from the outdoor cows in summer is much richer in anti-rickets vitamin than that from the indoor cows in the winter—a very important piece of information, as it leads us to realise that milk cannot be relied upon to contain any fixed amount of the vitamin, and so emphasises the need of supplementing it, particularly in winter, from more constant sources of fat-soluble vitamins such as cod liver oil.

In view of what we have said as to the interrelation between the anti-rickets vitamin and light it is interesting to consider the way in which some of the races of mankind are protected against rickets. Think first of all of the negro living in a tropical climate. He eats very little of the vitamin with his food, for this is mostly composed of vegetable products, and what fat he gets is in the form of vegetable oils, which are well known to be deficient in fat-soluble vitamins. But he is exposed continuously to a very intense sunlight that reaches him through a clean atmosphere, unpolluted with the dirt and smoke of an industrial community; he thus receives an abundance of ultra-violet light on to his scantily clad body and so is enabled to synthesise all the anti-rickets vitamin that he requires. In contrast to this take the case of the Eskimo who inhabits the extreme arctic north. He does not see the sun at all for most of the winter. But neither he nor his children show signs of rickets, for they eat such large quantities of seal flesh and whale blubber, and those often uncooked, that they receive a sufficiency of the anti-rachitic vitamin ready made in their food. Thus the prolonged absence of light does not affect them harmfully. It is very instructive, however, to notice that in cases where Eskimos have been tempted away from their native diet in favour of more "civilised" cereals and canned foods they have begun to suffer from harmful effects characteristic of vitamin D deficiency. But in general it may be

said that it is neither the "naked negro panting at the line" nor the fur-clad Eskimo shivering at the pole who is most liable to suffer from rickets: it is the dweller in an industrial town situated in the temperate zone. For he will not receive any too much of sunlight and what he does get will have been robbed of its most potent rays by having to filter through a murky smoke-polluted atmosphere. And he is the very man whose diet is liable to be made up to the largest extent of preserved and prepared foods from which the vitamins have completely disappeared, so that he will be in a position neither to manufacture the vitamin in his own body nor to receive it ready made with his food. It is therefore to the dwellers in industrial areas that this information about the anti-rickets vitamin is of greatest importance.

We cannot let pass this opportunity of pointing out that it is possible to do a great deal more than is actually done towards the maintenance of a clear atmosphere which will not rob the sunlight of its beneficial effects. Even if operating costs were slightly increased and profits correspondingly reduced, no factory should ever be allowed to discharge smoke and fumes into the air, and anyone who offends against this duty of keeping the air clean should be treated with no more leniency than one who knowingly poisons the food or drink of the community. By insisting on clean air that will let the sunshine through and ensuring a supply of the right kinds of food, rickets could be eliminated completely in the course of a year of two from among our infant population. We know how this could be done: surely it follows that we ought to do it.

From all that we have just said it will be realised that of recent years an enormous increase has been made in our knowledge of fat-soluble vitamins. In the case of the water-soluble vitamins B and C the advance has not been quite so spectacular. When we were describing the discovery of

vitamin B we said that it was known to be a substance "very similar to, if not identical with," the substance that Funk had extracted from rice bran—the substance, that is, which is necessary for the continued health of the nerves and the prevention of beri-beri. We made this somewhat vague statement intentionally, for although the water-soluble vitamin B which is necessary for normal growth was for a time thought to be identical with the anti-beri-beri substance, we now know that they are distinct substances although they usually occur together in the same food products. In order to express this fact the substance necessary for normal growth is sometimes referred to as vitamin B and that necessary for the maintenance of the healthy nerves as B_2. Other workers use the term vitamin B for the water-soluble growth-promoting substance and refer to the other as the anti-neuritic factor.

Then in addition to these there has been recognised during the last few years yet another vitamin belonging to the "B" group. This is the substance necessary for the cure and prevention of a disease known as *pellagra,* or "rough skin," that occurs among poorly-fed communities not only in southern Europe but also in the southern parts of the United States. In an exciting series of researches Goldberger has shown that this pellagra is due neither to an infection nor to a mere lack of good protein in the diet, but to the absence of a pellagra-preventing substance that is present in rich foods such as meat, eggs and milk, and, like the associated vitamins, is particularly abundant in yeast.

The other water-soluble vitamin, C, still retains its unity unassailed—that is, it has not been divided up into a number of separate substances each producing a different effect in the body. It still seems to be correct to regard it as a single substance with one specially important function, namely, the prevention of scurvy.

One of the most recent advances made in the study of vitamins has added a new member to the list. This is a fat-soluble substance called vitamin E, which seems to be necessary for the proper carrying out of the functions of reproduction. At all events it has been shown that rats of both sexes become sterile if they are deprived of this vitamin, although there seems to be no evidence yet that the same is true of human beings.

It would not be surprising if by this time some of my readers should say: "I never to my knowledge suffered from rickets during infancy, I am neither paralysed with beri-beri nor prostrate with scurvy—what then has all this to do with me?" To such an one I would answer that, quite apart from any interest or cultural value that the reading of this chapter up to the present point may have had for him, the information we have given may have some practical importance for him even although his life does not seem to be in immediate danger. For although there are quite a number of us who are free from the acute manifestations of these deficiency diseases, it is equally true that a very large proportion of people are suffering from slight degrees of vitamin deficiency sufficient to produce annoying and troublesome, if only minor, derangements of health. Let us illustrate this by means of a few examples. The fat-soluble vitamin A has been mentioned as essential for the normal growth of a child. But it has other actions in addition to this, its main and most obvious function. It seems that an individual, even an adult, who does not receive enough of this vitamin is particularly liable to colds and other chest infections. And to add to our list of horrors there is yet another disease that is liable to result from lack of a sufficient amount of vitamin A. In this case it is the eyes that are affected, and often so seriously that the sight is permanently lost. This happened among the children in Denmark during the later years of

the war when the Danish butter producers were exporting so much of their product to the belligerent countries that not enough remained for the population at home. The result was that they turned to margarine as a substitute; but this does not contain vitamins, and hence the outbreak of the malady. It quickly came to an end when an enlightened government rationed the butter supplies and so ensured that everyone received a proper share.

Then the other fat-soluble vitamin, D, is also needed not only for the prevention of rickets in children but for the maintenance of health in adults. For even when the skeleton has been properly formed and is fully grown the materials of which it is made are not permanent and unchanging, but are all the time undergoing small losses and replacements. If there is not an adequate supply of vitamin D in the body these processes of wear and tear are not properly balanced by those of repair, so that even in a fully grown adult person a softening and deformation of the bones is liable to occur, which leads to such pains in the joints that walking can be carried out only with difficulty if at all. This condition was prevalent among elderly persons in Vienna during the period of unsatisfactory food supply caused by the war, but disappeared promptly as soon as cod liver oil and other fats containing vitamin D were added to the diet.

Then there is a specialised portion of the skeleton in which the effects of a lack of vitamin D are also very serious. We refer to the teeth. It has been proved that these are just as dependent on an adequate supply of this vitamin for their normal development and continued health as are the bones. This gives us another reason why children should receive an abundance of this vitamin. When this idea was first put forward it received a considerable amount of criticism on the ground that, if it were true, bad teeth in children should be as common as rickets, since both are produced by a lack of

the same factor; while dentists reported that in their experience only a small percentage of the first teeth of children actually appear to be diseased. But then it was found that if one judges, not by naked eye inspection as the dentist usually does, but by a study of the detailed structure of the teeth under the microscope, not a small but a very large percentage of children's teeth are poorly formed, so that bad teeth do occur as commonly as rickets, although the abnormality may not be so obvious. It is not, however, only in children that vitamin D is necessary for the welfare of the teeth. Adults require it for the maintenance of their teeth, and it is even found that previously neglected teeth may be considerably strengthened by a change to a diet containing an adequate amount of vitamin-holding fats.

When we turn to the water-soluble vitamins we find exactly the same kind of story. Relatively few people are robbed of their vitamin B requirements to such an extent as to lead to a gross degeneration of their nerves, but nevertheless it seems likely that many of the minor derangements of health that are so widespread are due to a large extent to the taking of insufficient quantities of the vitamin B complex. The functioning of the alimentary canal seems to be influenced by one or both of the vitamins B_1 and B_2 and there is little doubt that much of the constipation that is prevalent in these days could be avoided if we were in the habit of eating more of the foods that contain these vitamins. Yeast has been proved to be specially rich in them, so that the modern propaganda for the use of yeast as a curative agent in these cases is not without its scientific foundation.

In these days there are so many causes for depression, fatigue and gloom that it is almost impossible to apportion the blame fairly among the various factors at work. But there is reason for believing that these undesirable symptoms are produced in some people by a long-continued lack of the

other water-soluble vitamin, C. Their diet is not sufficiently faulty to lead to unmistakable symptoms of scurvy, and yet it is sufficiently far from correct to keep them in a permanent condition of vague ill health.

It would of course be quite unfair to detail all the serious diseases that arise as a result of a lack of sufficient supply of vitamins without giving the reader some kind of indication as to how he can make sure of having a plentiful supply of these important substances in the diets of all for whom he has to provide. In order to achieve this, however, we must do more than merely list the commoner foods in which the vitamins are contained: we must give some indication as to the extent to which the vitamins contained in fresh food are likely to be lost or destroyed during the processes of cooking and preparing, and must try to indicate the amounts of each that our experience has shown to be necessary for the continuance of health.

The fat-soluble vitamins A and D usually occur in the same food-stuffs and so may be dealt with together. Most of us obtain a certain amount of these vitamins from milk, but we have already said that the vitamin content of milk is very variable and depends very largely on the conditions under which the cows are kept and fed. Milk from outdoor cows fed on pasture during the summer months, and also the butter and cheese obtained from it, will be richer in vitamins than winter milk and its products. Mere boiling of the milk does not destroy its fat-soluble vitamins but heating combined with exposure to air does, so that when milk has to be sterilised it is better to carry out the heating in a tall vessel, in which only a relatively small surface of milk is exposed, than to use a flat pan in which the air has much more chance of coming into contact with and destroying the vitamins. The making of dried milk powders also usually involves a considerable exposure of heated milk to the air, so

that one cannot be sure that these preparations, which are so commonly used for the feeding of infants, contain all the vitamins of the original milk unchanged. It will be readily understood that the amount of vitamins in ordinary beef and mutton fat will also vary according to the opportunity the animals have had for obtaining these substances for themselves, and that the process of frying in a shallow pan will tend to destroy such of the vitamins as these fats may have originally contained. Lard usually contains very little of the fat-soluble vitamins, and vegetable oils—olive oil in particular—are almost always devoid of them. So also, therefore, is the margarine that is manufactured from such oils. The standard source of the fat-soluble vitamins is, as the reader may have already guessed from our frequent mention of it in this chapter, cod liver oil, and the less refined, that is, the cruder it is, the more of the vitamins is it likely to contain. In order to ensure that infants shall receive enough of vitamins A and D to induce normal growth and to prevent the occurrence of rickets, cod liver oil should be given them every day after they are two or three weeks old. A couple of teaspoonsful of the oil per day seems to be sufficient for a growing child, although it is calculated that only about one two-thousandth part of the oil really consists of the active materials. Strange as it may appear to some people, infants will readily drink the crude oil provided the suggestion is never made to them that it is nasty. Frequent use is also made of preparations of irradiated ergosterol, although these do not really take the place of cod liver oil as they contain only vitamin D and no vitamin A.

Turning now to the water-soluble vitamins, the two vitamins B_1 and B_2 also usually occur in the same foods and so may be considered together. They occur characteristically in the materials that we use for making salads—lettuce, celery and tomatoes containing the largest amounts, although most

vegetables yield some. They occur together not only in the "polishings" of rice but also in the bran and embryo of cereals generally, so that brown bread and oatmeal porridge contain them. Milk also contains these vitamins and they adhere to the milk sugar when this is separated out. The value of yeast as a source of vitamins has already been mentioned, and this applies also to certain yeast extracts that are available on the market. It will thus be seen that quite a large number of foods contain vitamins B_1 and B_2 so that there is no great danger of anyone receiving too little of them, at least under normal conditions, particularly as these vitamins stand cooking fairly well. They are not much affected by boiling, but are destroyed fairly quickly at higher temperatures so that as a general rule canned foods will not contain them. The vitamin B complex differs from the fat-soluble vitamins in not being much affected by exposure to air.

Lastly to come to vitamin C. This is the vitamin that is characteristically present in fresh fruits—oranges, lemons, grape-fruit and tomatoes are the best sources of it—but it must be remembered that of all the vitamins C is most easily destroyed by heating and exposure to air during the processes of drying, preserving and cooking foods, so that as a general rule it is only the fresh, sound uncooked fruit that will contain it. There is one notable exception to this statement and this is furnished by the well-proven fact that whole tomatoes can be canned without loss of their anti-scurvy vitamin. Green vegetables, such as cabbage, contain the vitamin when they are raw but it is destroyed during the ordinary process of boiling. In this connection it is found that rapid brisk boiling destroys less of the vitamin than slow simmering, so that if it is necessary to preserve as much as possible of the vitamin C content of vegetables it is essential not to let them boil for several hours, as, for example, in making a stew. For the same reason other forms of slow cooking, such

as the use of the fireless cooker, are to be avoided. Of course if fresh fruit is included in the diet the loss of the vitamin from the vegetable does not matter; we are now speaking of cases in which, owing to difficulty of obtaining fresh foods, it is necessary to conserve as much of the vitamins as possible in the materials that are available. We have seen that the mere boiling of milk in order to sterilise it, and the heating and drying that are necessary for the preparation of powdered milk foods, also destroy the anti-scurvy vitamin that the fresh product contains. Naturally it is in winter and in isolated places that this question of the problem of the supply of fresh fruit, and so of the anti-scurvy vitamin is most acute, but modern methods of transport have done much to minimise the difficulties involved. From the point of view of the prevention of scurvy the practice of eating salads made with raw cabbage as a basis is thoroughly sound, and under difficult conditions the young plants obtained by the germination of wheat, peas, beans or other seeds could be eaten in the same way.

While it will be clear that the numerous facts about vitamins we have brought together in this chapter affect the health and well-being of all of us, they find their most important application in connection with the feeding of pregnant women, nursing mothers and infants. For the demands made on the mother's body during the formation of the child's new body and its nourishment afterwards by her own milk are so large that her need both for raw materials for the building up of the new tissues and for vitamins for the prevention of the deficiency diseases are far in excess of her requirements at other times. She has to receive enough, not only for herself but also for her child. And in addition to this it must be remembered that an error of nutrition committed during childhood may easily produce serious derangements of health whose effects will remain throughout life.

A period requiring special care is that at which the infant is weaned: while it is being suckled it will share the vitamin stores of its mother, and in this, as in so many other respects, it is found that the maternal organism is often sacrificed in order that the milk provided for the young shall contain the appropriate quantities of the required constituents. But when the child is being fed on artificial food mixtures it is entirely at the mercy of those who decide what its diet shall be, and in order to be a wise one that decision must take into account all the well-proven knowledge we possess on the subject. Now we have seen that apart from the amounts of vitamin D that are formed in the body on those all too rare occasions when it is exposed to direct sunlight, we have no power of making for ourselves the vitamins we require; we have to eat them ready formed. Expectant and nursing mothers must, therefore, be careful to eat liberally of milk, eggs, fresh vegetables, fruit, and the other vitamin-containing foods we have mentioned above. Accurate knowledge must take the place of superstition and ignorance. The old nurses' tale that if a mother eats fruit it will cause her milk to curdle in her breast must be ruthlessly set aside in favour of our certain information as to the absolute necessity of taking in a supply of anti-scurvy vitamin.

But not only the mother should be taken care of in this way: the child long before it is weaned should be given its own private vitamin supply. As we have already mentioned, a couple of teaspoonsful every day of a good brand of cod liver oil will furnish enough of vitamins A and D; the juice of an orange a day * will contain sufficient of C and some B, and if then the child does not thrive it may be because it is requiring still more of B which can be given in the form of yeast extracts. As growth progresses and the child grad-

* Notice that the orange has now replaced the "apple a day" which our parents used to regard as so effective for "keeping the doctor away." Apples contain only small quantities of vitamins.

ually passes to a mixed diet it should still be encouraged to eat plenty of foods containing the vitamins, and this in spite of any of those unreasonable and illogical dislikes for them that children sometimes show. At school age the need for vitamins still continues and those in charge of the diet of a school or similar institution should see not only that fresh fruits and uncooked salads are provided regularly but that each member of the institution partakes of them. It is not the amount of these articles *bought* that determines the health of the inmates; it is the amount *eaten*. It is quite evident that if some of the inmates persistently refuse fresh fruits and vegetables they will come to suffer from vitamin lack just as much as if these articles of diet were not provided for them.

So much then for practical hints on the application of our modern knowledge of vitamins. In giving it we have intentionally limited ourselves to mention of those foods that contain the various vitamins in greatest amount. But there are many other foods that contain one or other of the vitamins in smaller quantity, and by eating a correspondingly larger amount of such foods one can equally well satisfy one's needs for these substances. Practically all the common articles of food have been examined in this respect and anyone who is interested in the matter can easily obtain further information by referring to the works listed at the end of this book. In concluding our own account of the subject we will just mention that the study of vitamins is by no means at an end. Biochemists will not be satisfied until all the vitamins have been separated in the pure condition and their chemical constitutions have been worked out. They will want to know further their mode of action in the body and the exact way in which they are necessary for normal growth and health; they will doubtless also study the interaction of one vitamin with another and the modification of

their respective actions brought about by particular foods. There is, it will be seen, a very extensive programme of research ahead of us, and it will probably be a long time before all this desired knowledge is obtained. But it is equally probable that we shall not much longer be forced to eat particular foods in order to obtain this or that vitamin. Already as a preliminary to their more exact investigation great progress has been made with methods of separating and concentrating vitamins. Preparations, as we have seen, can now be made in which all the vitamin D of a specimen of cod liver oil is concentrated into about one thousandth of the original bulk of the oil, and the anti-scurvy vitamin of lemon juice has been concentrated to an even greater extent. All of which goes to suggest that we shall soon be quite independent of such foods as cod liver oil and lemons as immediate sources of these vitamins, and will soon be able to take them, if we wish, in the form of small amounts of the concentrated preparations supplied with our meals as salt and condiments are at present.

XIII

THE BIOCHEMIST VERSUS DISEASE

It might be said that the main theme of this book is to show that the fundamental processes occurring in the body are of a chemical nature—that is, that the properties and behaviour of the living matter can be to a large extent understood from what we know of the composition of its constituents and the changes that these are capable of undergoing when studied under various conditions outside the body. So far, however, we have dealt only with the constituents and processes of the normal, i. e. the healthy, body and have considered the various changes that must go forward in order that its health may be maintained. But at this stage it should not surprise the reader to learn that the same method of study may be made to yield information as to the changes that are occurring in the diseased body, and that the knowledge so obtained is of great significance in determining the means whereby its disease may be combated. We came very near to considering one aspect of this topic when we were talking about vitamins, but there we were considering the abnormal changes that are produced in an originally healthy body by the omission of these essential constituents from the diet, and were explaining the means whereby the deficiency diseases can be prevented.

But it all too often happens that even when the body is supplied with all of its essential requirements the life proc-

esses diverge from their normal course. Many such cases arise as a result of accident or gross mechanical damage to organs; in these the biochemist can offer very little help, for he is just as unable as the surgeon to provide a new normally-functioning organ, in the way in which an engineer supplies a new part to a machine. In other cases, such as *cancer,* for reasons that are still obscure to us, the cells of an organ grow and multiply to an exaggerated degree and produce growths or tumors that may encroach on vital organs and so bring the body to death. Under such circumstances all that the chemist can do is to provide accurate methods of analysis by which the chemical processes occurring in the body can be followed, so that from them an estimate may be made of the progress or subsidence of the malady. Perhaps the clearest example of this is furnished by *uræmia,* the disease in which the power of the kidney for secreting the waste product urea into the urine is to a greater or lesser extent interfered with. The biochemist cannot say what is the original cause of the disturbance of kidney function; the only contribution he can make is to determine exactly the amount of urea that has accumulated in the blood, and so furnish an accurate means of judging of the severity of the disorder. Many diseases are caused by the invasion of the body by bacteria and other micro-organisms; here the biochemist is playing a more and more important part, for he is studying the poisonous products given off from the invading organisms and is devising ways of neutralising their harmful effects. He is also studying the ways in which the body itself resists the attack of its enemies, and how it itself produces substances that tend to neutralise the poisons they liberate, so that he can already in many instances supplement these efforts towards recovery by sera and antitoxins of his own preparing. And he can even render persons who are liable to be exposed to certain infectious diseases, as, for example,

during an epidemic, immune to these diseases—that is, less likely to "catch" them—by injecting into them before they are exposed to the infection a good supply of these poison-neutralising substances. But the processes involved in these immunity reactions are far from completely understood; we have to rely on the sera and antitoxins produced by other living animals and cannot as yet make these materials in the laboratory, so that the biochemist is still unable to take the share of this kind of work that will probably ultimately fall to him.

But there are some cases in which the biochemist has already played a part of first-rate importance. These are the cases in which, as a result of derangement or disturbance of some organ, the body is producing in insufficient amount, or not at all, some particular substance that it ordinarily manufactures for its own use. At present we are unable to say what are the causes of these departures from normality, and so are powerless to prevent them. But as we are about to see in detail, a careful study of the chemistry of the abnormal body has suggested means whereby we at least go a long way towards curing these disorders even if we cannot achieve their prevention. For in quite a number of such instances the biochemist has been able to make the lacking substance artificially outside the body, and then to supply it to the patient so that his lack may be compensated and his condition brought back to one of normal health.

Having thus become acquainted with the general principle involved in such cases, let us now consider the matter a little further. In the first place, what *are* these substances produced in the body which are so essential to well-being that a diminution in the supply of them leads to the onset of disease? The reader may at first think that we are referring to the digestive juices, for certainly these seem to answer to the description. Produced by the various digestive glands, they

subserve the supremely important function of the digestion of food, and any failure of their supply is fraught with the gravest consequences so far as the nutrition of the body is concerned. But it is not of these that we wish to speak. We wish rather to explain that the glands that produce the digestive juices are not the only ones the body possesses. Among others we could mention the sweat glands of the skin and the milk glands of the breast: all these have this in common with the digestive glands, the fact that they pour their secretions into some space that is *outside* the actual body tissues; they are glands of *external secretion.* There are still other glands that produce characteristic products but do not send them out through a duct to some remote place; they pass them into the blood as it circulates between the secreting cells so that these products are ultimately carried to all the tissues of the body. It is to these glands of *internal secretion,* which secrete into the body itself, that we wish to devote particular attention at the present moment.

In order to make our ideas definite let us take as a first example the gland known as the *thyroid.* Most people have heard of it, and many will know that it is situated in the neck. When we examine its structure we find that it is made up of little vesicles of secreting cells, but we discover no trace of a duct to lead away the secretion that these cells produce. What we do find is that this organ has a very abundant blood supply, and it is evidently in the blood as it courses through the gland that the gland products are carried away. And once in the blood stream these products will be carried to every place to which the blood has access, which means, of course, to practically every cell in the body. In this way the products secreted by the gland can influence the chemical processes occurring in the body as a whole, and hence can determine to a greater or lesser degree its growth, behaviour and condition.

We have long known the part played by the products secreted in this way by the thyroid gland in establishing and maintaining the normal health of the body. For occasionally in a child the thyroid may be either entirely absent or very imperfectly developed. Such a child fails to grow up; its body remains stunted and undeveloped, and its mental powers will be about equal to those of a normal child of as many months as it itself is years of age. In isolated country places such a person becomes the village idiot, or, as the French call him, the *crétin;* the derangement from which he is suffering is therefore called *cretinism.* As soon as it was realised that in such cretins the essential abnormality is that the thyroid gland is not functioning sufficiently, it was an obvious step to try to make up this deficiency by supplying the characteristic thyroid material from other sources. Experiments soon showed that the removal of the thyroid by operation in young animals leads to the same kind of retardation of development that is observed in a cretin, so that it is evident that the thyroid has the same kind of function in other animals as it has in ourselves. The next thing was, therefore, to determine whether the thyroid product could not be obtained and administered to human cretins from the glands of animals slaughtered for food. And this hope was fully and successfully realised. It was found that if a person whose own thyroid is deficient receives in his food an appropriate amount of the thyroid of, say, a sheep, his deficiency is made good, and he can, at all events in the majority of cases, grow and develop as fully as a normal person. The only requirement is that he shall receive a continuous supply of thyroid throughout his life. Nowadays the biochemist has made this requirement much easier to fulfil, for he has shown how the active substance in the gland can be concentrated into a powerful extract that can be kept for a long time without deterioration, and so can be always available under conditions

where a continuous supply of the fresh gland might be difficult to secure.

In order to continue our study of the active principle of the thyroid gland we must now mention another disease in which this organ is involved. It is not uncommon, especially in some localities, to find persons in whom the thyroid gland has become enormously enlarged until it forms a large ugly swelling or *goitre* on the neck. As we have said, this malady occurs most commonly in certain districts, and when the matter is looked into it is found that these districts are usually tracts of country either remote from the sea or sheltered by mountains and other natural barriers from the sea breezes. Now by chemical analysis it has been shown that the thyroid is remarkable among the organs of the body for the relatively high percentage of the element *iodine* that it contains—of course not in the free condition but in chemical combination. Our ordinary articles of food have only small traces of compounds containing iodine, but the thyroid gland has an amazing power of accumulating these small traces of iodine and of using them for its own purposes. As we shall see later, the essential constituent of the thyroid secretions is a compound of iodine, and if the gland does not contain the small amounts of iodine it needs, it undergoes this process of excessive overgrowth that leads to the production of a goitre.

Now the small quantities of iodine contained in our food are in general derived from the soil on which that food is grown, and for the replenishment of its own small but essential iodine stores the soil depends on those small but ever present traces of iodine compounds that are borne by the wind in the spray that is carried off from the sea. It is a matter of common knowledge that the sea contains relatively large quantities of iodine salts, and that marine plants store up large amounts of these salts so that, until other more

available sources were discovered, the whole supply of iodine was at one time manufactured from the ashes of particular kinds of sea weeds. It is a proven fact that the vegetables, milk and other products raised on soil of mountain valleys that are effectively cut off from the sea breezes contain much less iodine than similar products originating from more exposed localities. We can thus understand how it is that goitre should be so prevalent in these sheltered areas, and why, therefore, this disease presents a more serious problem in a centrally situated country like Switzerland than in countries possessing a seaboard. Fortunately, now that we have this much information on the subject, the preventive measures required are simple both to understand and to apply. All that is necessary is to ensure an adequate amount of iodine in the diet, and it has been found most convenient to do this by adding small quantities of iodine salts to the ordinary table salt that is used by the community. And this has proved to be of such value that in Switzerland it is now illegal to place on the market salt that has not been iodised to the prescribed degree. But these traces of iodine are of vital importance not only to human beings; as would be expected they play a similarly important rôle in the well-being of other animals, and on this account this question of iodine supply has had in some instances a considerable influence on the stock-raising industry. For there were at one time large tracts of land out in the middle western states where cattle would not thrive. When the functions of the thyroid gland came to be understood it was soon realised that the cattle in these districts were suffering from thyroid deficiency produced by a lack of iodine. Evidently the soil and vegetation of those parts of the country are deficient in this element, for when small quantities of it were added in the form of iodides to the drinking water supplied to the cattle, it was

found that they could be raised as profitably there as elsewhere.

When all this had been realised—when it had been firmly established that for the normal development of the thyroid and for the production of its important secretion iodine was necessary—attempts were made to find out exactly what was the particular iodine compound that is manufactured by the gland and that exerts such an important influence on the growth and health of the body. It is only recently that these efforts have been crowned with success, but in the last year or two methods of extraction have been found that enable the active iodine compound to be isolated in a pure condition from the thyroids of slaughter-house animals, and once the pure substance had been isolated the determination of its chemical composition and constitution followed almost as a matter of course. It turns out after all that in spite of earlier views to the contrary the active substance produced by the thyroid (and named on that account *thyroxine*) is an iodine derivative related to an amino-acid called *tyrosine*. And not only has this been proved by analysis but the conclusion has been confirmed by the building-up or synthesis of the substance by well-understood chemical reactions from compounds of well-known chemical constitution. It might have been thought that so complete a knowledge of this active substance and the ability to manufacture it artificially in the laboratory would have rendered us independent of the supplies of it from animal sources. But it is just one example of the complicated relationships involved in this kind of work that when the artificially prepared thyroxine is administered by the mouth it is not absorbed at all easily from the alimentary canal, and so at present cannot be used to replace the natural thyroid extract for curative purposes. It seems as if in the natural gland extract there are substances

accompanying the thyroxine that keep it in solution or in some similar way assist in its absorption into the blood stream. At present studies are being made of some of the artificially prepared near derivatives of thyroxine in the hope of finding one that, while still showing the same useful physiological action on the body, will be easily absorbed when given with the food.

The functions of thyroxine in the normal body will be already clear to the reader from what we have said about the abnormal effects that result from a lack of it. In a general way it may be said to be a great accelerator of life processes, and more particularly of those of growth, development and metabolism. One very interesting way in which its influence on growth can be shown is to administer it to tadpoles by giving them thyroid gland as food. It is then found that they develop much more rapidly and undergo their metamorphosis into frogs much sooner than other tadpoles taken from the same batch but given just ordinary meat.

Quite apart from the extreme pathological cases we have mentioned, the relatively small differences in the amount of thyroid secretion produced by different individuals often show themselves as differences of personal temperament. The person who produces too little thyroxine is generally of a slow and lethargic disposition and he tends to grow fat: in him the fire of life is burning only slowly. On the other hand, the individual who produces rather more than the normal amount of thyroxine will be restless and overexcitable: his heart will beat fast and he will usually remain thin. The difference between these two individuals is again brought out when we compare the rate at which combustion is taking place in their bodies by measuring their rates of basal metabolism (see pages 74 and 77). The person with excess of thyroid activity will have, even when he is com-

pletely at rest, a higher rate of basal metabolism than would be expected in a normal person of the same size and body area. The metabolic rate of a person with diminished thyroid activity is, on the other hand, correspondingly low. In fact, this is what we had chiefly in mind when on an earlier page we discussed basal metabolism measurements in medical diagnosis, one of the principal uses of these measurements being to detect the beginnings of abnormalities in the functioning of the thyroid.

Owing to the action of thyroxine in promoting the metabolism of the body, thyroid extract has been much used for the purpose of reducing weight by persons who from one cause or another show too great a tendency to embonpoint. But this use of thyroid is highly dangerous in the absence of expert medical advice, for thyroxine exerts a stimulating action on the whole of the body metabolism: it does not merely encourage the combustion of fat but facilitates just as much the burning up of more useful and essential materials, such as tissue proteins, so that although an obese person may actually lose weight as a result of taking thyroid extract this loss may be due to removal of essential body constituents as much as to removal of excess fat that the body has stored. And further—seeing that obesity may arise as a result of a number of different causes apart from thyroid deficiency—the person who suffers from it may, and probably will, already possess a normally functioning thyroid, so that when he (or more usually she) takes more thyroid for reducing the fat the harmful effects of excess of thyroxine are liable to be produced.

We have chosen this example of thyroxine and discussed it at some length because it constitutes a very clear-cut example of the way in which the modern biochemist plays an important part in the prevention and cure of disease. Here we have an organ, the thyroid, that normally produces a sub-

stance without which neither normal growth nor health of the body is possible. In some individuals owing to some abnormality the thyroid does not function properly and its important secretion is not produced. The biochemist comes to the rescue and determines what substance it is that the gland produces, he extracts the substance, isolates it in a pure condition and then proceeds to determine its chemical constitution. He then sets about finding some way in which he can synthesise the substance—some way, that is, in which he can manufacture the material in his laboratory without having recourse to the living organism, and when at last he has succeeded in this he can supply the artificially prepared material so that those who are not producing enough of it in their own bodies can receive it from outside, and so be enabled to lead normal healthy lives instead of sinking into a condition of permanent abnormality and disease.

We are going on, in a moment, to consider another very important case in which this kind of chemical help has been successful, but before we do so we would mention that the thyroid is by no means the only gland that is busy supplying an internal secretion to the blood. There are in the body some six or seven small organs whose functions were long a mystery. In addition to the thyroid we have the tiny little *parathyroids* embedded in the main mass of the thyroid itself; we have the curious *pituitary body* that is formed by the union of a little bit of the lining of the roof of the mouth (which becomes separated off and gradually works its way below the surface) with a downgrowth from the under side of the brain, the complex little organ so formed coming to lie embedded in the bone of the floor of the skull; we have the *suprarenal bodies* that lie, as their name suggests, just above the kidneys, and a number more of organs or at least masses of tissue scattered about the body.

Now some of these organs possess quite definitely the

type of structure that is usually associated with the function of secretion, but as no one of them possesses a duct, the function of all of them remained very obscure until the possibility was realised that they poured their products into the blood. Now the substances that these glands pass in this way into the blood are carried round and exert very powerful actions on many of the processes of growth and activity in all the tissues, so that these internal secretions do not always confine their effects to particular organs but often influence in a very profound manner the condition of the whole body. From the fact that some of them exert a stimulating action and bring organs into a condition of activity these substances are also referred to as *hormones,* from the Greek meaning "I excite", although it would not be true to say that all of the substances included under the term hormone produce excitement and activity when they arrive at a given organ; in fact in some instances the opposite is the case. We may regard the hormones as drugs, so to speak, that are produced normally in the body, in its glands of internal secretion, and that have the function of influencing the development and growth and well-being of the body as a whole, or of assisting, by their effects on particular organs, in the carrying out of one or more of its functions.

There is no need to point out the marked effects produced on the behaviour of an individual by drugs that he takes into himself from outside sources. It is not surprising that in an exactly similar way the drugs he is continuously producing within himself, in his glands of internal secretion, take a very large share in determining the manner in which he reacts to various circumstances, that is, in moulding his behaviour. To a very large extent we are the men and women that our glands make of us. Now it is often found that the influence of the secretion produced by one gland is opposite to that produced by another, that between the two secretions a mutual antago-

nism exists. One hormone, for example, will tend to make the body grow tall, another will tend to stunt it, and the final stature of the individual will be determined, at all events to a large extent, by the exact balance existing between the quantities of these growth-stimulating and growth-inhibiting hormones that are circulating in his blood. And the same sort of thing is true of other body functions besides growth. Of course we have not here given a fundamental explanation of the differences in behaviour and stature we find between individuals, for, while it is true enough that these manifestations are determined by the hormone balance, what we have said gives us no clue to the reason why the hormone balance of one individual should be different from that of another.

With these general remarks about hormones and the kinds of things they are and do, we shall now go on to consider more specifically a hormone that has received a very large amount of attention of recent years on account of its relation to that deadly disease, *diabetes*. The mere mention of the name of this disease is sufficient to let most people know that it is *insulin* we are about to discuss, so very widespread has been the rejoicing that this potent agent for the relief of the disease has at last been obtained in a form suitable for administration to sufferers. But let us begin at the beginning of the story. It has been known for quite a long time that the essential feature of diabetes is that the patient loses sugar continuously in his urine. Unlike a normal person, the diabetic cannot utilise the sugar that is contained in a normal diet or is formed from its other carbohydrates by the process of digestion. According to the severity of the case a smaller or greater quantity of the sugar remains unused and simply circulates in the blood until the kidneys treat it as they would a foreign substance or waste product and filter it off into the urine. This loss of sugar is not in itself such a very serious matter: it means that so much of the food

is wasted, but, as we have seen, the body can use other materials besides sugar as fuel in the tissues—fats can be so used, and so can any excess of protein that is eaten over and above the amount that is required for making good the wear and tear of the tissues.

But it so happens that the burning of fat and the burning of sugar in the body are processes that are not completely independent of each other. It has been definitely established that if a certain amount of sugar is not being burned in the body, then fats cannot be burned completely either. And when we say that they are not burned completely we mean that their carbon is not all converted by union with oxygen into carbon dioxide, and their hydrogen is not all converted into water. A certain amount of the fatty acids is broken down by partial oxidation into half-way products which fail to undergo the further complete oxidation to carbon dioxide and water to which they would be submitted in the normal body—that is, in the body which was at the same time burning sugar. This further waste of the fuel supply of the body would also in itself not be so serious were it not for the fact that these half-burnt products derived from fats are poisonous substances and are very harmful in the body. For one thing they are somewhat strong acids, though their poisonous action is greater than can be accounted for by their acid properties alone. A person need not be a diabetic patient in order to know what it feels like to have these poisonous acids formed in his body and circulating in his blood. For they are produced whenever sugars are not being burned in the body, and we can most easily establish this condition by withholding sugars and all substances that are digested down into sugars (starch, for example) from the diet. This would give us a diet composed entirely of proteins and fats: it could be made up of fat and lean meat, butter, eggs, sardines and the like, but no bread or potatoes.

Without trying the experiment, the reader will feel instinctively that a spell of a few days on such food would make him thoroughly ill, and now he knows the reason why it would. When sugar is not being burned in normal amount in the body the fats are only incompletely burned and the products of their incomplete combustion are poisons. This has been expressed by saying that so long as there is a bright fierce fire of sugar the fats are consumed cleanly, but when the carbohydrate fire dies down the fats only smoulder and produce a noxious smoke. In the case of experimentally produced carbohydrate starvation the harmful symptoms can be promptly removed by adding sugar again to the diet. Such poisonous products as are then in the body are soon removed and no more are formed. But in the case of diabetes these poisonous half-oxidation products of fats usually accumulate in greater and greater amount in the body, and unless suitable steps are taken they will ultimately bring the patient to death in a condition of coma (unconscious collapse). Nor is this all, for although the tissues cannot use sugar they, so to speak, demand it, and in their attempt to obtain it there is produced in the body a kind of reaction in which all available materials are converted into sugar. Even the proteins of the tissues suffer this fate: it is well known that several of the amino-acids obtained by the breakdown of proteins can form sugar in the body, and in the diabetic patient it seems that an attempt is made to utilise this possibility. But it is all to no purpose—the sugar that is formed in this way cannot be any more utilised in the patient's abnormal body than that supplied with his food. The net result is that he is worse off owing to the loss of his tissue proteins, and that he is wasting away at the same time as he is being slowly poisoned.

These facts about diabetes were soon and easily established when it became the subject of scientific investigation, but no one knew what is fundamentally wrong with a dia-

betic—no one could say how it is that he cannot utilise sugar like a normal person, until in 1889 two German scientists hit upon the extremely important discovery that when the pancreas is removed from an animal sugar appears in its urine. This was practically an accidental discovery, for they were not expecting to find sugar in the urine of their experimental dogs, and indeed were not looking for it; but it so happened that some of the urine of one of their experimental animals had dried up, leaving a little mass of crystals, and their laboratory servant finding these had curiosity enough to taste them, and was astonished at finding them sweet. From the moment this discovery was made it was evident that the pancreas plays an absolutely fundamental part in the normal use of sugar by the body, for not only did the dogs operated on by von Mering and Minkowski waste sugar in their urine, but they ultimately died in a condition of coma brought on by the accumulation in their bodies of the poisonous products of the incomplete oxidation of fats. In other words, by removing the pancreas from an animal it is possible to imitate the very conditions observed in a human subject suffering from diabetes. And it was not long before the clinicians began to find that at least in the majority of cases the pancreas of a diabetic patient when examined after his death shows distinct signs of abnormality or disease.

In our chapter on digestion we had a great deal to say about the pancreas and the important digestive juice that it secretes, and it might at first sight seem that the disorder of diabetes is due to some failure in the production of one or more of the pancreatic enzymes we then mentioned. But that this is not so was soon proved by studying the effects produced by simply tying the duct of the pancreas so that its juice could not pass into the intestine while the organ remained otherwise intact and in its normal position in the body. When this was done it was found that no symptoms of

diabetes were produced at all, and that the animal that had undergone this operation differed from a normal beast only in its diminished power of digesting its food. The utilisation of sugar in the body therefore proceeds normally in spite of the absence of the pancreatic juice, so that it is quite clear that the pancreas does not influence this utilisation by means of any of the substances it passes into the intestine. The only other possibility is that it exerts this influence by means of some further substance, not yet mentioned, which it sends to the tissues by way of the blood stream. In other words, the pancreas maintains a normal utilisation of sugar in the body by means of a hormone that it produces. That this is so has been confirmed by a number of various observations. It has been shown, for example, that if the pancreas be cut right out of the body and then grafted in again in some abnormal position, say under the skin of the belly, and if the graft "takes" and new blood vessels grow into it so that its cells remain alive (it would otherwise degenerate and become slowly absorbed), no diabetes results, because, although the pancreas cannot under these circumstances carry on its digestive function, the production and distribution of its hormone are not interfered with. Another interesting case arises when a female animal from which the pancreas has been removed becomes pregnant. This experiment was carried out on a dog and it was found that in spite of the complete absence of pancreas from the mother she did not develop diabetes, because the hormone produced in the pancreases of the embryos she was carrying diffused in sufficient quantity into her blood to keep her in normal health. But later when the pups were born her supply of the hormone failed and diabetes supervened.

Now when we make a careful examination of its structure we find that the pancreas is one of those many "double" organs that we find so commonly in the body. We mean by

this that it is composed of two quite distinct kinds of tissue mixed and bound up together to form one compact organ. The most obvious tissue in the pancreas is, of course, the secreting tissue that forms the pancreatic juice, but we have in addition to this masses or "islands" of another kind of tissue scattered through the substance of the gland. In these islands the cells are not arranged in the way in which we usually find cells that produce an external secretion arranged; they are not associated with a duct or its branches but abut on to a rich network of blood vessels. These islands of cells must therefore be the structures that manufacture the internal sugar-regulating secretion of the pancreas and pass it into the blood as it courses through. For this reason, as soon as physiologists were convinced that it must exist, but long before it had been isolated in a potent form by the method we are about to describe, this internal secretion received the name *insulin*. It is important and interesting to find that in the early stages of the development of an embryo the cells that produce insulin are quite separate from those that produce the pancreatic juice and only later become associated with them. In some animals, moreover, the two kinds of cells remain quite separate throughout life.

It was only natural that, as soon as it had been made certain that these islands produce a hormone necessary for the proper combustion of sugar in the tissues, attempts should have been made to prepare an extract containing this hormone in a form suitable for administration to a patient for the cure of diabetes. But no very certain success attended these first efforts, not only because it proved difficult to obtain extracts free from unwanted extraneous materials that were distinctly poisonous, but mainly because in extracting a pancreas one is extracting not only the hormone-producing cells but also those that produce the powerful digestive enzymes, and these appear to be able to act on insulin and

destroy it. We have here a special kind of difficulty which is not encountered in the production of a potent extract of the active material of the thyroid gland.

In 1922, however, Banting and Best of Toronto hit upon the idea that perhaps it would be possible to overcome this difficulty if they tied off the duct of the pancreas and then left it in the body of the animal for some time before making the extract: this tying of the duct prevents, as we have already mentioned, the passage of the pancreatic juice into the intestine, and this in turn leads to a degeneration of the cells that produce the enzymes of the juice, but it does not harm the insulin-forming cells, so that if we wait long enough before using the pancreas we obtain for our extraction an organ that contains only the cells whose product we desire. These experimenters lost no time in putting their idea to a test and the day on which they showed that it is possible in this way to prepare an extract which, when administered to a diabetic patient, provides him with the very material that his body lacks, was a momentous one in the history of medical science. From the Toronto laboratory the glad news of the latest triumph of biochemical science spread like wildfire and laboratories the world over set to work to study the possible ways of making this precious extract and to work out in detail its action and effects.

It soon became evident that although the Toronto workers had really obtained the substance necessary for the cure of diabetes, their original method of preparing it was too complicated and specialised to be of use in manufacturing insulin in the amounts that would be required if it was to be generally available to all who stood in need of it. Other sources of insulin soon suggested themselves. It was found possible, for example, to obtain an active preparation by taking the pancreas of an unborn embryo, in which the enzyme-forming cells are not yet active; and also by col-

lecting the "islet" tissue from fishes which is readily accessible as it remains separate throughout the life of the animal and does not become associated with the digestive portion of the pancreas as it does in ourselves and other land animals. It was even found possible to obtain substances that have an action similar to that of insulin from plants. But no one of these sources was available to the extent necessary for the manufacture of insulin on a commercial scale. What was wanted was some method of extracting the insulin from the pancreas of an ordinary animal slaughtered for food, some way, that is, of avoiding the harmful effects of the digestive enzymes contained in such material on the hormone it was desired to extract. It did not take long to discover that ordinary slaughter-house pancreas could be used as the starting material, provided that, instead of water or weak salt solution, dilute alcohol was used for the extraction. This causes the enzymes to be safely precipitated out of the way without harming the insulin. The alcohol can then be removed and the extract further purified and concentrated until it is suitable for administration to a patient. This method of alcohol extraction at once became the standard method of manufacture of insulin and at the present time practically every country has its own factory where this process is employed.

In using insulin for the cure of diabetes we are employing a principle exactly similar to that involved in the use of thyroid extract for the prevention of cretinism and other disorders due to interference with the normal production of the thyroid hormone—that is, we are supplying from outside a substance that the body is failing to produce for itself, but which it must have if normal health is to be maintained. But in the details of the application of this principle there are some important differences between the two cases. In the first place, we do not yet know the chemical constitution of in-

sulin, so that, unlike thyroxine, it cannot be synthesised in the laboratory, but must be extracted ready formed from the organ that produces it. Then again, as we have so often mentioned, insulin differs from thyroxine in that it is destroyed by the digestive action of the enzymes of the alimentary canal, so that it is useless to administer it by the mouth. It has to be injected under the skin by means of a hypodermic needle which is a little troublesome although, of course, quite simple. Then lastly, when insulin began to be used on a wide scale it was soon discovered that it must be administered with some care as the effects of an overdose are quite serious. The hormone assists the body to burn sugar, and if too much of it is present the sugar can be used up so completely that it practically disappears from the blood. But unless the blood contains some sugar the cells, more particularly those of the nervous system, cannot maintain their normal functions; they send out uncoördinated impulses that lead to convulsions, and then cease to function altogether, so that a condition of unconsciousness and collapse supervenes. The dose of insulin must therefore be very carefully regulated according to the needs of the patient at the time, being increased if he eats more sugar and diminished if his sugar consumption becomes reduced or if there is reason to suspect that his own pancreas is beginning to acquire the power of producing insulin for itself. But fortunately, should too much insulin be given, it is quite easy to counteract its harmful effects by giving a liberal dose of grape sugar to compensate for that of which the body has been inadvertently robbed. Incidentally this effect of excess of insulin is very useful in one way for it gives us a method whereby we can estimate how strong any particular preparation is, and this is obviously very important if we are to be able to administer it in properly controlled doses. We cannot separate out the insulin and weigh or measure it directly but we can get an idea of the amount of

it present by the intensity of the effects it produces on some suitable animal—that is, we can protect our patients by trying out our insulin on the animal first. The animal usually used for this purpose is a rabbit, and the unit of insulin at present in use is taken as that amount which will reduce the concentration of sugar in the blood of an animal weighing 4 lbs. to such an extent that it shows convulsions in two hours. A larger amount of the hormone will produce this effect more quickly, a smaller amount more slowly or not at all.

We have given the reader a fairly full account of this insulin not only because its separation is one of the most recent and striking triumphs of biochemical skill, but also because its employment has brought so much benefit to suffering humanity. Admittedly we have not been able by its aid to cure diabetes in the sense of enabling a patient to make the hormone for himself again; still less have we been enabled to define or to prevent the pathological change that is responsible for the failure of the supply in the first instance, but by the continuous administration of the hormone from outside sources we have enabled patients who would otherwise be condemned to a slow lingering death to resume a life of normal activity and usefulness.

We will now say just a little about another hormone which, although perhaps not so important as thyroxine and insulin for the cure of disease, nevertheless finds some application in medical practice, and in any case is interesting as being the first of the hormones to be isolated and synthesised. We refer to *adrenaline,* the characteristic product of the little yellow suprarenal glands which we have already mentioned as being situated near the kidneys. When an extract of these glands is injected into the blood of an animal some very definite and characteristic effects are observed. The heart beats more quickly and forcibly, many of the small blood vessels—especially those running to the alimentary canal

—become partly closed up so that the walls of the other vessels are simply stretched and bulging with the extra amount of blood they have to contain—in other words, the blood pressure is increased. Among other effects that take place we should notice that any movements occurring in the alimentary canal would be brought to rest, and that the pupil of the eye would be widely opened. Physiologists have traced all these active effects to the general stimulation of one of the important systems of nerves that control the involuntary functions of the body, but as biochemists we are not particularly concerned with this. What does interest us, however, is that some of these effects of adrenaline are of great use in medical practice. It gives the surgeon a means of closing up small blood vessels and so of diminishing bleeding during operations, and, even more important, it gives him a means of stimulating the heart and maintaining its activity should it show signs of failing in a patient who has had to be kept under the influence of an anæsthetic for a long time. As we have said, the chemical constitution of adrenaline is well known and the substance has been prepared artificially in the laboratory. Various closely related synthetic derivatives of adrenaline have also been studied and some of these are now being employed with advantage in place of the parent substance itself. At this stage it will no longer come as a surprise to the reader to learn that the effect of a substance on living tissues can be very closely correlated with its chemical constitution, and that small changes in that constitution lead to corresponding changes in the details of physiological action, so that by suitable small changes of chemical constitution artificial drugs may be prepared whose action on the body is more appropriate for some purposes than that of the naturally-occurring substances.

All the actions of adrenaline which we have enumerated form a group of manifestations that together make up the

complex response of the body to violent emotions such as anger or fear. When we are really angry our hearts beat faster, our blood pressure rises until we nearly "burst a blood vessel", the small superficial arteries of the skin close up until our faces blanch with our rage, and our eyes dilate and start from our heads. All these reactions together bring the body into a condition suitable for making a violent effort of attack or defence, and as they can all be produced in the body by the injection of adrenaline it is thought by most authorities that during such times of stress adrenaline is actually passed into the blood in relatively large quantities and so is responsible for the stimulation of the various nerves by which these reactions are produced. Indeed, some would even go so far as to say that the temperament of an individual is determined by the ease with which adrenaline is turned out from his suprarenal glands under the influence of strong emotion, the equable even-tempered man having his adrenaline output well under control. Others have even ascribed national characteristics, and with them the difficulties of international relations, to the same cause. In other words, we have here another case where personality seems to be determined by the hormone balance of the body.

Before we close this chapter we will refer to one other organ extract because like adrenaline it is very useful in surgical practice, although we know far less about it from the biochemical point of view. We have already mentioned the complex little pituitary gland that lies at the base of the brain. This seems to produce quite a number of hormones that together have very profound effects on the growth and functioning of the body. Of these effects we will mention only one, namely that of causing contraction of all the involuntary muscles of the body. It is for this purpose that the extract of the gland, which is on the market under the name of *pituitrin,* is most commonly employed. When, for example, during

child-birth the contractions of the uterus are not so vigorous as they should be, it is the custom to give an injection of a little pituitrin in order to stimulate the involuntary muscles concerned to greater activity. But what is the active material present in this extract, and whether indeed it does not contain more than one active substance, no one at present can say.

From these examples the reader will now have some idea of the way in which the biochemist is investigating the powerfully acting drugs that are to be found in living matter; how he is gradually working out their chemical constitutions and finally synthesising them in his laboratory and so providing the physician with materials which are required for bringing a diseased body back to health. He can, as we have seen, go even further than this and by synthesising new products, related chemically to those originally isolated from living organs, he can often improve on the naturally-occurring drugs and provide the physician not only with the particular materials to supply to a patient, who through some abnormality is failing to produce them for himself, but also with substances by means of which he can produce specific reactions in the body and so combat the symptoms of disease. And there are not lacking those who, indulging in speculations as to the part played by the scientist in the future of the human race, foresee the time when not only will the obviously abnormal persons whom we call patients be benefited by such administrations, but also the mentality of those whom we should now call normal persons will be influenced in the same kind of way—when the personality of an individual will be controlled by special products elaborated for the purpose in biochemical laboratories! The day may even come when the biochemist by a judicious application of his potent artificially-prepared drugs will be able to convert us all into the most charming of people. But that day is still a long way off and meanwhile he has graver problems to wrestle with.

XIV

THE CYCLE OF NATURE

THE story of this, our final chapter, begins with a point arising out of what we said about the digestion and utilisation of protein food by the body. In discussing this subject we said on page 136 that the proteins of the food become finally digested down to amino-acids; that these amino-acids are absorbed into the blood and by it are carried round to all parts of the body; and that it is from these amino-acids that the tissues build up the new proteins they require. It will be seen that in the whole of this process there is no formation of new amino-acids in the body; the amino-acids that are used by the various tissues already existed combined together in the proteins of the food. Now as the human race increases in numbers more and more material must be being used to form the proteins of human bodies, and as the body itself cannot manufacture the necessary amino-acids they must all be taken in as proteins in the food. It becomes, therefore, a matter of no little interest and importance to inquire what is the original source of all this material from which new human protoplasm is made. It does not help us very much to realise that our main supply of amino-acids is obtained from the proteins of meat and other animal products, for our food animals, just like ourselves, are unable to build up amino-acids from the elements of which they are composed—oxen, sheep and pigs require

amino-acids ready formed just as much as we do. Now these animals are entirely vegetarian in their diet, so they must obtain from the constituents of plants the amino-acids from which they build up the proteins of their tissues. When we use their tissues as food we take these proteins to pieces again and re-combine the pieces in new ways in order to form our own personal proteins, so that it follows that all the amino-acids composing human proteins were once constituents of the living matter of plants, and may have come to us after a temporary sojourn as constituents of the proteins of a sheep, a pig or an ox. All the amino-acids in all the living matter in the world must therefore have been obtained from plants. Truly in this sense "all flesh is grass." Even the fish of the sea are similarly dependent, directly or indirectly, on marine vegetation for the amino-acid units they require for building up their tissues.

But now we have to inquire whence the plants obtain amino-acids. Apart from those relatively rare cases in which plants have degenerated into nourishing themselves on the materials elaborated by other organisms, the food materials that a plant requires are very different from those demanded by an animal. The animal as we have seen must have foodstuffs that are composed of complicated substances such as proteins, fats and carbohydrates. The plant, on the other hand, will grow and thrive on the simplest of diets; in addition to air and water it requires merely small quantities of such simple inorganic substances as nitrates, phosphates and ammonia and traces of such mineral substances as lime, potash and iron. These inorganic materials are under ordinary circumstances absorbed with the water that the root of the plant takes in from the soil. Apart from providing a firm mechanical support this supplying of inorganic materials is the only function that the soil serves in the life of the plant, and it is quite easy to grow a plant entirely in water if we

take care to dissolve in it the necessary small quantities of the substances we have named. The reader may like to try it for himself. The necessary solution is made up according the following formula:

Potassium nitrate (saltpeter)	1.0 gram.
Sodium chloride (common salt)	.5 gram.
Calcium sulphate	.5 gram.
Magnesium sulphate (Epsom salt)	.5 gram.
Calcium phosphate	.5 gram.
Iron chloride	a trace
(Enough iron will be obtained if an ordinary iron nail is kept in the solution.)	
Water	2 pints

Any druggist can supply at a small cost the mixture of solid materials which can then be dissolved all together in the proper quantity of water (preferably rain water) at home. It should be noticed that the calcium phosphate will not dissolve completely but will settle down as a sediment or precipitate at the bottom of the liquid. A two-pound jam jar is a convenient vessel in which to carry out the experiment: it must be fitted with a cork or wooden cover with a hole about half an inch in diameter in the centre. Through this hole the roots of the plant are carefully passed so that they dip into the solution in the jar. The hole is then packed loosely with cotton wool round the stem so that the plant is suitably supported but has space for growth. The plant itself may be of almost any kind, but a young wall-flower seedling is as suitable as any. Of course in any case it must be a seedling and not a fully grown plant, otherwise we shall not have an opportunity of observing its growth. In order to make the conditions a little more natural the jar should be covered with a layer of thick brown paper so that the roots are kept in the dark. If now the jar be placed in a window where it

will receive plenty of light and air it will be found that the young plant will thrive and grow at least as vigorously as a similar one planted in the ordinary way in soil, and can be made to come to maturity and produce flowers and seeds if the solution in the jar is renewed, say, once a week as its dissolved constituents become used up. All this will probably remind the reader of growing hyacinths and other bulbs in glasses of water, but there is this important difference: in the case of a bulb the materials it requires are already stored up in the leaves and other parts of the miniature plant it contains, and the further development of this plant involves little more than an expansion and unfolding of the leaves and flowers already present. But a young seedling of such a plant as a wall-flower has practically no stored reserves; it has to depend entirely on the materials we supply in the solution in which it is grown.

Now the amazing thing is that the plant can go on and grow and produce its new tissues and all the complicated substances that these contain when we appear to supply it with so little in the way of raw materials. For example, the proteins and starches and sugars that its living cells contain are all compounds of carbon, and yet we have included no carbon compounds of any kind in the solution in which the plant has grown. The only carbon compounds to which the plant has had access are the small quantities of carbon dioxide that exist in the air, and it is from these alone that it has had to build up all the complicated materials of its tissues. Now the amount of carbon dioxide in ordinary atmospheric air is only about 3 parts per ten thousand, and when the idea was first put forward that plants obtain all their carbon from the air it was at once objected that there was far too little carbon dioxide to provide all the enormous amounts of carbon that would be contained, for example, in a forest of trees. But then it was soon realised that by the action of the

winds the air is kept so constantly stirred up that, small though the percentage of carbon dioxide is, the large total amount of it existing in the whole atmosphere is really available for the use of the vegetation of the earth. And as soon as it was shown that plants could be grown so successfully in "water cultures," in the way in which we have recommended the reader to try for himself, the old idea that plants derived carbon from the soil had to be completely abandoned. In the same way it will be seen that the plant is quite independent of any complicated nitrogenous materials there may be in the soil: it takes in its nitrogen in the form of the simple inorganic materials—in our experiment as nitrates. We thus see the enormous and fundamental difference between the way in which plants and animals nourish themselves. The animal must have food that, chemically speaking, is relatively complicated—amino-acids, sugars and such things, or materials that yield these on digestion—while the plant can build up these complicated materials practically right from their very elements. The plant starts almost at the beginning with the building up of the complex substances that form its tissues; the animal cannot do this but has to take advantage of this work of synthesis that plants carry out.

Now if it is true that the plant obtains the whole of its carbon from carbon dioxide, and that it builds up from this simple substance such things as sugars, starches, fats and ultimately proteins, several important consequences arise. In the first place it is evident that the plant must in this way obtain much more oxygen than it needs, for carbon dioxide contains a much greater proportion of oxygen to a given amount of carbon than does any of the products that the plant makes from it, so first we have to find out where this oxygen goes to. In the last decade of the eighteenth century it was discovered by that very learned English churchman, the Reverend Joseph Priestley, that if mice or other small

animals are kept in a confined volume of air in a jar they collapse after a certain length of time (as we now know for lack of oxygen) but that the air can be renewed and again rendered fit for supporting animal life if green plants are allowed to grow in it for some days. Priestley did not explain this important result in quite the same terms as we use today, but he realised clearly that there is a fundamental interrelation between the plant and animal worlds, the plants adding continuously to the atmosphere that constituent (now called oxygen) which the animals need, and removing from it that constituent (now called carbon dioxide) which they produce, thus keeping the composition of the air constant.

It will not be at all difficult for the reader to convince himself that plants do give off quite large amounts of oxygen, and in the hope that he will try yet another experiment we will give him the full instructions for it. In order to be able to collect the oxygen most easily it is convenient to use some kind of plant that normally grows under water. The most accessible is the common Canadian water weed that is to be found in abundance in all streams, but a handful of practically any green water plant will do. Water cress will also serve. Bring it home and keep it in water until you are ready to use it. Next it is necessary to provide some water containing enough carbon dioxide to enable the plant to grow vigorously. The easiest way of doing this is to use the carbon dioxide that you yourself are producing. Take a tube of some sort and bubble your own expired air through a large bowl of water until you are tired of it: you cannot overdo it. Next take a glass jar, say a one-pound jam jar, dip it into the water until it is *quite* full and then turn it upside down without letting the mouth come up above the water. In this way it will remain quite full of water; if it does not, if there is an air bubble in it, it is necessary to try again. Now it will be possible to pass the pieces of water weed down into the

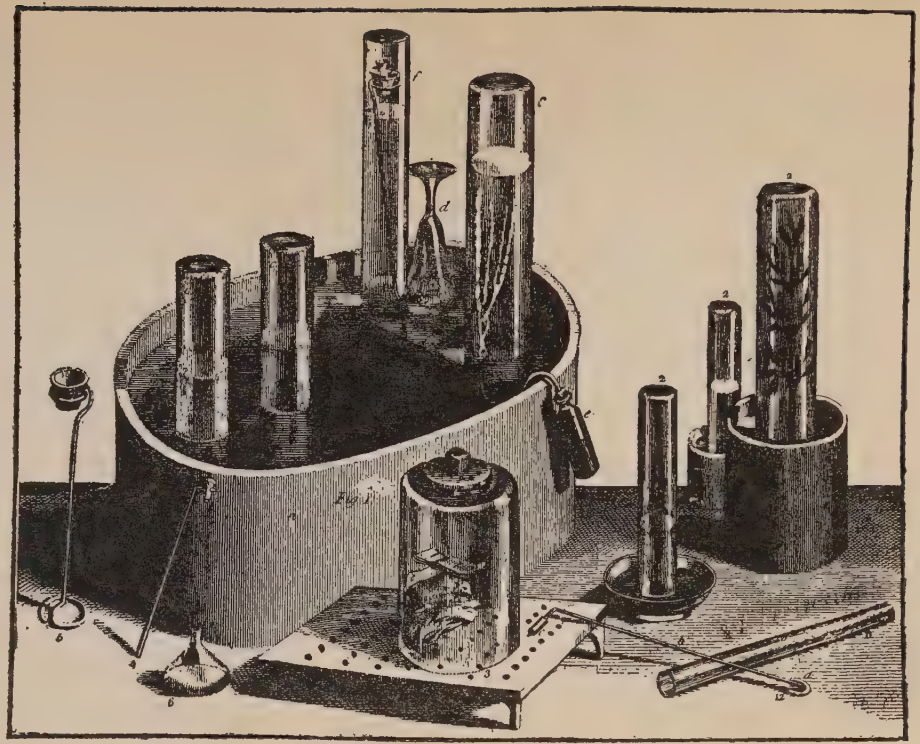


FIGURE 6. Apparatus used by Priestley for studying the changes produced by animals and plants in the composition of the air.
(Courtesy of Messrs. Heffer and Sons.)

bowl and up into the jar without letting in any air bubbles: do this until the jar is comfortably but not tightly filled with the plant. Now take a saucer, let it also down into the water, bring it up to the inverted mouth of the jar and lift the jar and saucer out of the bowl together, with the jar standing upside down in the saucer. This takes a long time to describe but in reality is very simple. Be sure to take a bowl that is large enough to enable you to work conveniently, and if you are new to those manipulations have a practice run without the plant. When this simple little apparatus has been successfully loaded up you will have an arrangement practically identical with that which Priestley himself used to use, and which is shown in figure 7 taken from his book entitled *"Experiments and Observations on Different Kinds of Air"* published in 1775.

Place your apparatus in a window where it will receive as

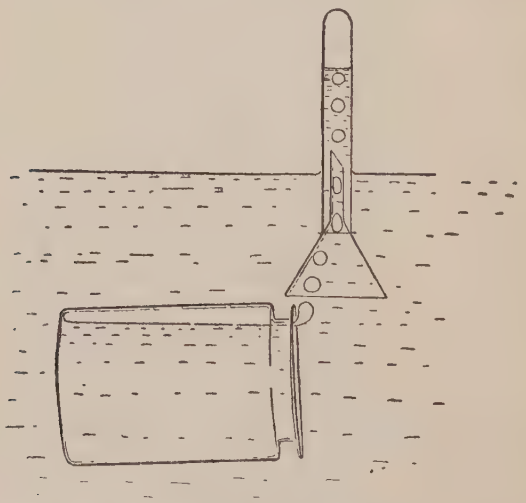


FIGURE 7. Method of transferring a gas bubble from one vessel to another under water.

much sunlight as possible and after a few hours you will already be able to see that a bubble of gas is collecting at the uppermost end of the jar. If you examine it carefully while the sun is actually shining on it, you will even be able to see the gas streaming off in minute bubbles from the broken ends of the stems of the plant. It may easily take you a week or more to collect as much of this gas as is convenient for testing; that depends on the brightness of the weather. If you can collect a quarter of a jar-full that will be more than enough. Now in order to examine the gas it is necessary to transfer it to a more suitable vessel—an ordinary test-tube will be best—and in order to get the gas from the one vessel to the other a small glass funnel will be required. The drug stores will be able to supply both of these. To carry out the actual transfer of the gas it is necessary to have a large tub or bath of water. In this fill the test-tube completely with water and invert it just as you did the jar at the beginning of the experiment; bring the funnel under the test-tube with the stem projecting up into it and then give it to somebody to hold under the water. Meanwhile you yourself should lower the saucer and jar of weed just as they are into the water and then take the saucer away. You can now pull out the weed bit by bit and at the same time shake any bubbles of gas that may be sticking to it up into the jar. Now bring the jar near the funnel and slowly and carefully bring it right side up so that the bubble of gas passes up along the side of the jar and then passes out to be caught by the funnel and so transferred to the tube. If this is strange to you you can easily practice with another jar containing a bubble of ordinary air before you try with the gas collected from the plant. It is a kind of pouring upwards, (see figure 7). When the gas has been successfully transferred, take away the funnel and close the end of the tube with your thumb. Now ask your assistant to bring you a splint of wood that has been lighted and then blown

out so that a good-sized spark remains on the end. When you are certain that the spark is strong enough to last, take up the tube (still closed by your thumb) out of the water, turn it right side up so that any still in it runs to the bottom and the gas comes to the top. Then bring the glowing splint close up to the mouth of the tube, gently slide away your thumb and at once thrust the splint into the tube. If the experiment has been successful the spark will immediately blaze up vigorously, thus proving that the gas you have collected from the plant is really the supporter of combustion, i. e. *oxygen*. There is just one more thing to notice, which is that the experiment will not succeed unless the plant remains in healthy condition the whole time. If it begins to rot no oxygen will be obtained: oxygen is given out only during the normal growth of the plant.

Thus we have proved that, so far as their exchange of gases with the atmosphere is concerned, plants and animals form counterparts of one another. The animal burns up carbon and forms carbon dioxide, the plant absorbs the carbon dioxide and uses the carbon but gives back the oxygen, so that the life of both plant and animal may continue. We should emphasise the point that the experiment just described could have been carried out with *any* green plant: we chose a water plant by way of illustration because it is easiest to collect the gas it gives off without getting it mixed with air.

Now when we were talking about the production of energy in the body we pointed out that when carbon burns to form carbon dioxide a very large amount of energy is set free. It follows, therefore, that when the carbon and oxygen in a plant are again separated as we have described, this same amount of energy must be re-supplied. For otherwise we should be obtaining energy for nothing, and that is contrary to all human experience as summarised in the principle of

the conservation of energy. We must therefore ask ourselves where the plant gets this energy from. It is a matter of common knowledge that plants will grow only in the light, and in describing our experiments on plants we have always directed that they should be kept in the window in order to get as much light as possible. It is evident that light plays a very important part in the life of the plant. It is quite easy to show, by repeating the "oxygen" experiment we have just described, but this time keeping the jar of weed in a dark cupboard instead of in a lighted window, that the light is absolutely essential for the decomposition of carbon dioxide and the liberation of oxygen: for no gas will be obtained from the plant kept in the dark. From this we see that it is from the light that the plant obtains the energy required for taking carbon dioxide to pieces, and that in this way it has the power of storing up as chemical energy some little fraction of the enormous amounts of energy that the sun is all the time showering on to the earth as light and heat.

Now the capture and storage of energy play such an important part in the affairs of the world to-day that when we find that plants, in spite of their apparent passivity, have solved this important problem there is no need to emphasise the need for finding out as much as we can of the way in which they do it. For not only the plants themselves, but we and the rest of the animal creation, are absolutely dependent on the sunshine that they thus store up. In our description of the last experiment we mentioned especially that it was necessary to use a *green* plant, and this for the reason that if we try the same thing with a plant or a part of a plant that is not green (with heads of flowers, for example) we find that these have no power whatever of decomposing carbon dioxide and liberating oxygen. On the contrary, such non-green plant tissues can easily be shown to take up oxygen and pro-

duce from it carbon dioxide just as an animal does. It is therefore the green colouring matter which the plant possesses that enables it to absorb the energy of sunlight in this way. This "leaf green" or *chlorophyll* as it is called (from the Greek words χλωρος, light green, and φυλλον, a leaf) serves not merely to add a predominating tint to terrestrial landscapes, it plays an extremely important part in the life of the vegetation. That it does actually absorb energy from sunlight is easy to show, for, as it happens, chlorophyll is very readily dissolved out of leaves by means of alcohol, so that we can quite easily obtain a solution of it to experiment with. It is necessary to place the leaves (a handful of the grass mowed from a lawn serves quite well for the purpose) in a jar and to cover them with denatured spirit and leave the whole to stand for a few hours in order to obtain a beautiful green solution of chlorophyll in alcohol.

Most people know how, by means of a prism of glass, a beam of white sunlight can be spread out into a coloured band or spectrum in which all the colours of the rainbow are represented—red, orange, yellow, green, blue, indigo and violet, all in order. Now if we place a solution of chlorophyll in the path of the beam of sunlight and then allow the light that comes through the solution to pass through the prism, we find that not all of the various coloured lights are to be found in the coloured spectrum we obtain. We shall at once notice that in particular the red light is missing and that a black patch occupies its place, showing that the light of this colour has been held back or absorbed by the chlorophyll solution. In the same way we shall notice, although perhaps not quite so readily, that the blue is also absorbed. Thus it is not the whole of the mixture of coloured lights making up white sunlight that is taken up by the chlorophyll, but only the red and blue constituents. Indeed, that is why the

substance appears to us as green: when we look through its solution our eyes receive not the whole of the white light that is entering the liquid but only the colours that are left over when the red and blue have been absorbed, and of these remaining colours the most conspicuous and abundant is the green. Now light is a form of energy, and when it is absorbed by a substance such as chlorophyll this energy is retained. In our experiment with a chlorophyll solution the absorbed energy went simply to heating the solution slightly, but in the plant it is converted into the chemical energy required for the decomposition of carbon dioxide.

We must now consider this decomposition of carbon dioxide a little more closely, for it is not quite so simple a matter as may have been supposed from the casual way in which we have referred to it so far. The carbon dioxide is not just broken up into oxygen and free carbon; what really happens is that it enters into a series of chemical changes in which the oxygen is actually liberated but the carbon never appears as such—it is at once built up into complicated substances which require energy for their formation and which are capable of giving back this energy when they are burned, i. e. when their carbon combines with the atmospheric oxygen to give carbon dioxide again. The intermediate steps of this utilisation of carbon by the plant are not very easy to follow but there is no difficulty whatever in demonstrating, at all events, one of the chief end products, for it is that common substance, starch. Perhaps the most instructive way of doing this is to prove that starch is formed in a green leaf when this is exposed to the light, but not in the dark. Take some quick-growing plant, such as a geranium. If it is in a pot, leave it in a dark cupboard for a couple of days in order to get its leaves starch-free. If it is growing in the ground, gently wrap one of its healthy leaves in tinfoil for the same length

of time. Meanwhile from another piece of tinfoil cut out any easily recognisable design that suits your fancy—preferably something not too complicated—simple letters or something of that style. At the end of the two days wrap this stencil round the selected leaf in such a way that only a part of the upper surface of the leaf is exposed through the stencilled design: the leaf of course must not be damaged and must remain attached to the plant in order to be kept alive. This is most conveniently done in the morning. Now arrange this leaf so that it is exposed to bright sunlight for the

FIGURE 8. Starch formation in a leaf.

whole of the day—six hours at least. At the end of this time we want to test for the presence and distribution of starch in the leaf. To do this pick the leaf in the evening and place it first in boiling water for a few seconds and then in denatured alcohol for a few hours or overnight in order to dissolve away the chorophyll. Then simply dip it into a solution of iodine such as was used when we were studying the digestion of starch by saliva (page 119). If the experiment

has been successful the area of the leaf that was exposed through the stencil will take on a deep blue colour while the rest of the leaf, the part that was in the dark under the tinfoil, will remain white, thus proving not only that starch is one of the chief products formed in green plant tissues, but also that it is formed only when these are exposed to the light. Figure 8 illustrates the result of a typical experiment carried out in this way. By using an ordinary negative in place of a stencil it is even possible to print a photograph on a leaf in this way. A large nasturtium leaf serves very well for this purpose.

We might here point out that, while starch is manufactured in the cells of the leaves it is usually stored in quite another part of the plant—in the seed, for example, as in the case of the wheat grain, and in a swollen underground stem, as in the case of the potato. Now the method whereby the starch is transported from the place where it is made to these storage depots or other parts of the plant where it is required, is interesting because it involves a process of digestion of the starch very similar to that which takes place in ourselves. The starch is formed and laid down as grains in the cells of the leaf, and, as more and more of it is produced, it is added layer by layer until the starch grains have the characteristic lined or striated appearance we mentioned in Chapter III. But such starch grains could never pass through the walls of the cell in which they are formed; in order to make them, or rather, the material of which they are composed, transportable they are acted upon by a ferment very similar to ptyalin and are so converted into sugars, which being soluble in water can soak or diffuse through the walls of the cells and can be transported in solution through the tiny little tubes that form a network in all parts of the plant. When starch is to be stored, this sugar solution is taken up by the storage cells and from it starch is once more formed and laid down

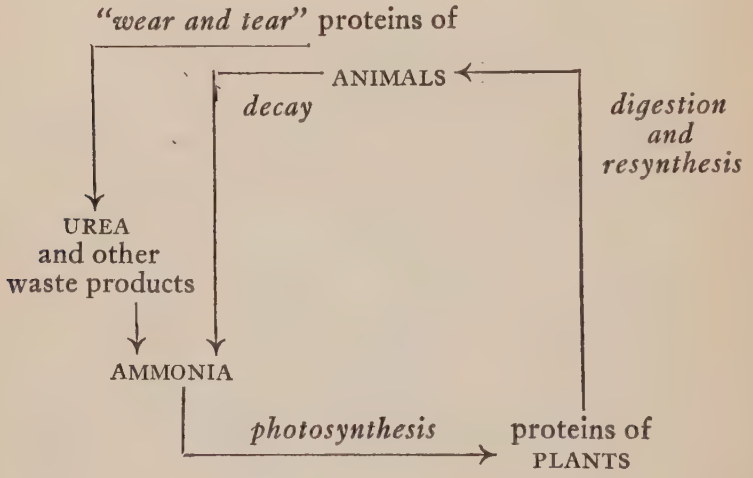
again as grains. This same process of digestion of starch takes place during the germination of a seed in which starch is the food stored up for the needs of the young growing plant. This fact is made use of in the manufacture of beer. Barley is spread out on a floor and kept damp and warm: the grains soon begin to germinate and the starch with which they are packed, in preparation for being transported and used, is converted into sugar. When this process of digestion has gone on for an appropriate length of time the malt, as it is now called, is extracted with water and so there is obtained cheaply and easily a solution of sugar which can be fermented by means of yeast.

We have discussed this formation of starch by the plant at some length partly because of its intrinsic importance and partly because it is a process that the reader can so easily demonstrate for himself and so need not take on trust. We depend on this production of starch for much of our food and drink and for the fine white stiffness of our linen, apart from a host of other minor benefits. But starch is by no means the only complicated substance that a plant is able to build up. Think of all the colours and scents that plants produce and of the many useful drugs they provide us with. We began this chapter, moreover, by pointing out that all the proteins in all the living things in the world owe their existence to the synthetic powers that we find to be such an accomplishment of the vegetable kingdom. Now for the formation of all this protein, nitrogen is obviously required, and we have already seen that the relatively small amounts of nitrates and ammonia in the soil are sufficient to supply all the nitrogen that a plant uses for this part of its chemical activity. This being so, it becomes a matter of great importance to consider what are the ways in which nitrates and ammonia find their way into the soil at all, and to consider the processes

in which the stock of these nitrogen-containing substances in the soil is kept up.

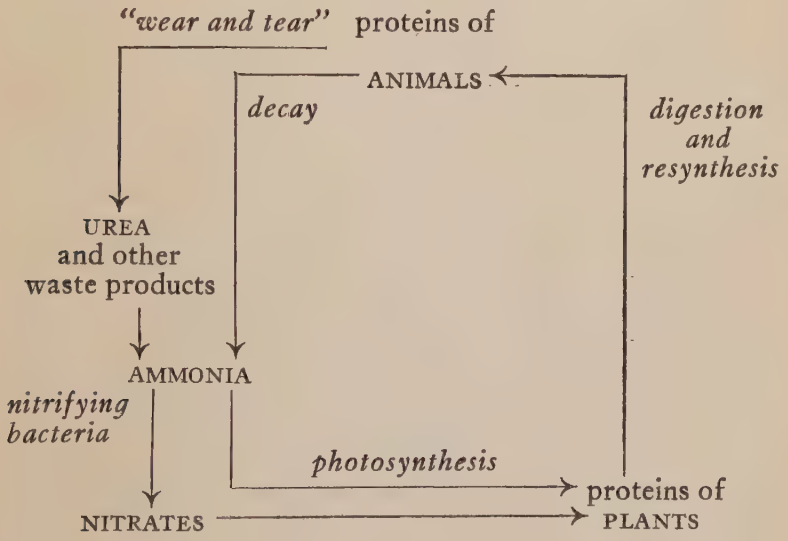
One main source of supply is from the nitrogenous substances that animals produce as waste products. Throughout its life an animal's tissue proteins are breaking down by those processes of wear and tear that we have spoken of, and the nitrogen that was once part of the animal's living stuff is got rid of in the urine in the form of urea and other nitrogen-containing substances. Under ordinary conditions this urea finds its way into the soil, but it does not remain there long in an unchanged condition. For there occur everywhere, in air and earth alike, bacteria that have the power, thanks to an enzyme they contain, of breaking up urea and forming ammonia from it. Everybody is familiar with the pungent ammoniacal smell of stables and will now realise why the sweepings from them are so useful as a manure for the purpose of enriching the nitrogen stores of the soil. But it is not only throughout its life that an animal is contributing nitrogenous materials to the soil. When the creature dies its carcass may be preyed on by other beasts, who utilise the materials for building up their bodies. When these in turn succumb to the inevitable fate of all living things they will probably furnish nourishment for maggots and such lowly forms, which in their turn will form the food of bacteria and similar simple organisms, and these will complete the final breakdown of what was once a beautifully organised system of complicated proteins into such simple substances as ammonia and carbon dioxide. And from these simple beginnings the plants start on the task of building up again those unique and exquisite materials that are necessary for the manifestation of new life. It will now be realised what we mean when we say that an organism during its life merely "borrows" the materials of which it is made. Those same materials were

used many times already by other organisms before it, and at its death it will yield them up again to that great store of material from which new life is constantly being elaborated. Thus the main chemical operations of Nature work in a cycle, nothing is permanently lost, and as one idol crumbles another arises from its ruins. In cold scientific fashion we can represent and summarise these ideas in a diagram like this:



Now in this scheme we have represented the plant as obtaining all of its nitrogen from the ammonia that we have thus traced into the soil. But if the reader will turn back to page 247 he will be able to remind himself that in our "water culture" experiment we raised a plant completely and successfully in a solution in which the only source of nitrogen was potassium nitrate (nitre or saltpeter), and as a matter of fact it is probable that under ordinary conditions plants obtain the greater part of their nitrogen not from ammonia

but from nitrates present in the soil. But these nitrates that fertile soil contains are formed from the ammonia that finds its way into it. Ammonia is a chemical compound of nitrogen and hydrogen, while in the nitrates the nitrogen is combined with oxygen. Now in the soil there are crowds of bacteria that are capable of oxidising away the hydrogen of ammonia, and so producing nitrates while utilising the energy liberated in this change for their own life processes. In this way are obtained the nitrates that plants use, and in order to make our diagram more complete we must add another step to represent this process. We thus obtain:



Long before anything was known about these micro-organisms their nitrifying activities were utilised in an old-fashioned method of manufacturing saltpeter which used to be practised in countries with a sufficiently warm and dry climate, such as, for example, the South of France. It con-

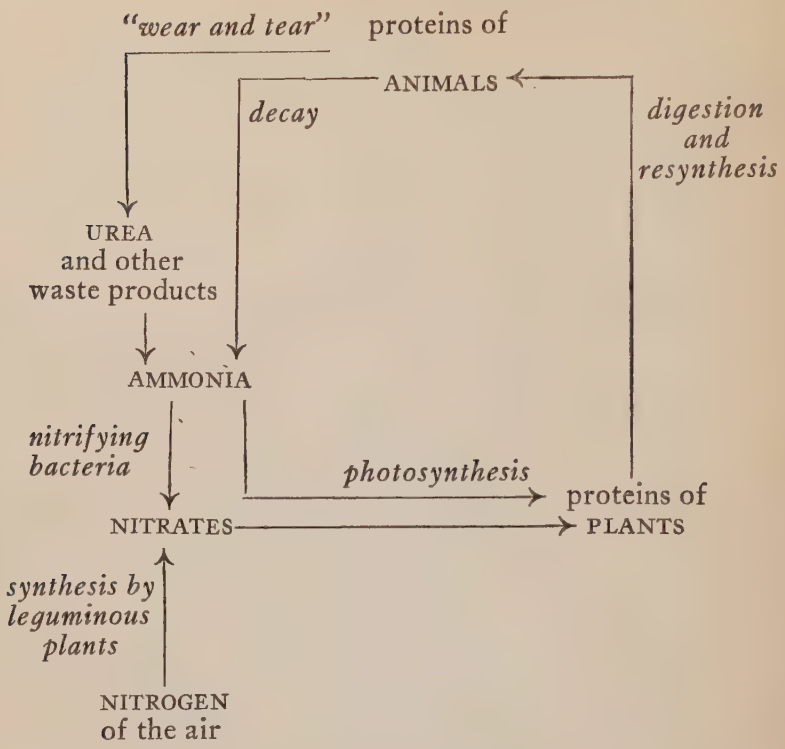
sisted in collecting large piles of dung and other animal refuse mixed with wood ashes and allowing the mass to stand and decay in a warm sheltered place with occasional raking over so as to introduce air. Under these conditions the ammonia formed by the decomposition of the nitrogenous constituents was gradually converted by the bacteria into nitric acid and this at once combined with the potash supplied in the ashes to give saltpeter (nitrate of potash) which was finally dissolved out of the mass by water and recovered by the evaporation of this solution.

But even now we have not yet exhausted our account of all the sources of nitrogen compounds to the soil. In general, of course, if we take a crop from a field we leave the soil impoverished and it is not capable of yielding so good a crop again until it has been manured with materials that can replace those that the plants of the first crop used. But it has been known for a very long time—in fact it was known to the old Roman farmers—that this is not true of all crops; that one can take some crops off a field and yet leave the soil *richer* than it was before. Examples of such crops are peas, beans, clover, vetches and other plants that belong to the leguminous family, that is, to the family of plants that bear their seeds in pods or legumes. We now know that this is because the plants of this family are more or less independent of any nitrogenous substances that the soil may contain, for they are capable of obtaining the nitrogen they want from the enormous supply of it that exists in the air. They really begin at the *very* beginning in their synthesis of living stuff.

Now this is a very surprising thing indeed, for we have been careful to point out what a dull, lazy, inert element nitrogen is, so that when we find that there are plants that can induce it to do anything, to enter into any kind of chemical

combination at all, the matter is worth looking into. As a first step in the investigation of this phenomenon it was soon discovered that all those plants that can utilise atmospheric nitrogen have numbers of curious little swellings on their roots. Then it was found that the plants in question do not themselves utilise the nitrogen directly, but that the swellings on their roots contain colonies of a special kind of bacterium that can take up the nitrogen gas and convert it into nitrates for the use of the plant. We can now understand the advantage that is gained by the *rotation of crops* which has been practised as long as agriculture has been the subject of observant interest on the part of man. It has for long been the custom to grow a crop of a leguminous plant on land that has been under wheat or similarly exhausting crops for some time. The leguminous crop leaves the soil charged with those useful nitrogen-fixing bacteria by which its nitrate stores are replenished, and thus its fertility is restored. And if the leguminous crop is afterwards ploughed in, as in the practice known as "green manuring," the land has the double advantage of receiving not only the nitrogen-fixing bacteria and the nitrates they make but also the ammonia formed when the vegetable matter decays, for the nitrogen of plant proteins, like that of animal proteins, appears finally as ammonia when the plant organism dies. At one time it was thought that it would be very useful to make special cultures of these nitrogen-fixing bacteria for use as fertilisers, but the idea has not been used very extensively owing to the abundance of other sources of ammonia and nitrates for the purpose.

In view of all that we have said about this direct utilisation of the atmospheric nitrogen by the leguminous plants, we can now add another line to our diagram of the circulation of nitrogen in Nature, thus:

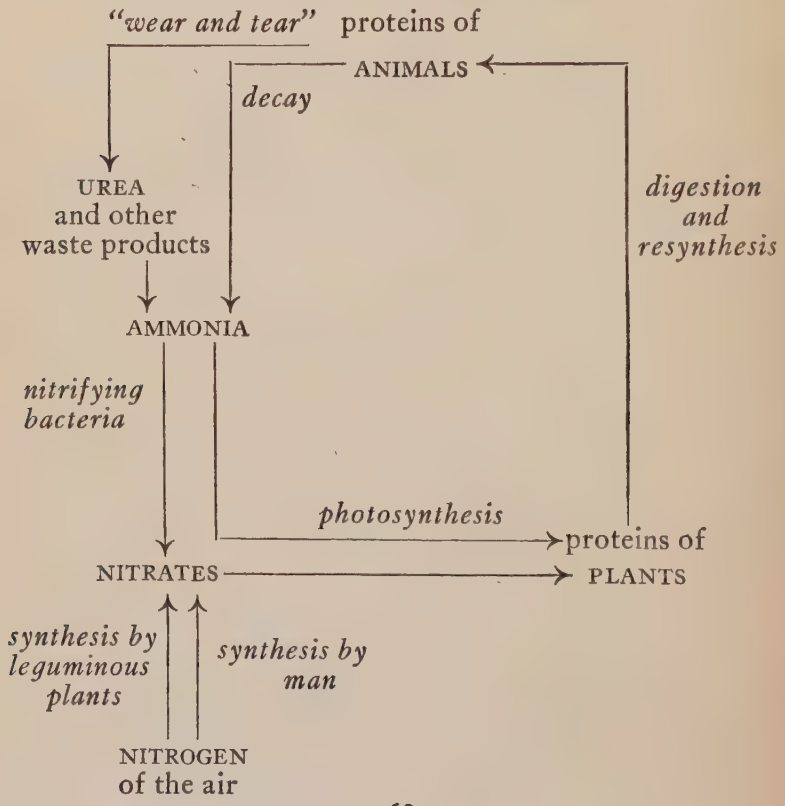


Although the subject perhaps strictly belongs rather to the realm of pure chemistry than to that of biochemistry, it is not uninteresting to consider the various ways in which man endeavours to maintain the nitrogen supply of the soil he cultivates. After all, though nitrates and ammonium compounds are not in themselves living matter, from what we have already said it will be evident that our very lives depend on a never-failing supply of them. In the first place we have available the vast deposits of naturally-formed nitrates that are found in some parts of the world, notably in Chile.

This "Chile saltpeter" is a product of prime importance to agricultural practice. We have also deposits of other nitrogenous materials which can yield ammonia when acted upon by micro-organisms of the soil. The chief of these is *guano,* which is really the dried excrement of birds accumulated during vast ages. But most of this is now used up. Then a not unimportant part of the ammonia used for manuring is obtained as a by-product in the distillation of coal for the manufacture of gas. Coal consists of the remains of the forests of huge tree ferns that flourished millions of years ago in the age known to geologists as the Carboniferous. It was the age at which the first land-living animals made their appearance, leaving their remains in the rocks. When we distil this coal and obtain from it ammonia as one product, we are merely recovering some of the nitrogen that once formed part of the proteins of the living matter of these ancient plants. But it is being more and more clearly realised that all these supplies of nitrogenous substances for agricultural purposes are really limited in quantity, and, enormous as the stores of them may be, it is only a matter of time before they become exhausted.

Chemists have, therefore, cast jealous eyes on the practically unlimited stores of nitrogen in the atmosphere and have tried to devise processes by which they could imitate the powers of the leguminous plants and "fix" the nitrogen in a form in which it could be used by other crops, such as wheat. It would take us much too far from our main topic to discuss these processes in detail: some of them aim at the production of ammonia by the direct union of nitrogen and hydrogen; others manufacture a product that will slowly form ammonia in the soil; but the most spectacular method of nitrogen utilisation actually burns the nitrogen and oxygen of the air together in an enormously powerful electric flame, and so produces nitric acid directly. And these processes are by no

means in a merely experimental stage. During the war hundreds of thousands of tons of nitric acid were produced in these ways in Germany, and the peace-time production is on such a scale that there is little doubt that we could rely upon it entirely if there ever arose a shortage in our other supplies of fixed nitrogen. We are therefore justified in giving a place to these human efforts at nitrogen fixation by representing them by yet another line on our diagram thus:



The electrical energy used for these synthetic processes is usually obtained from waterfalls and such inexhaustible sources of cheap power.

Before we leave this topic of the cycle of nitrogen in Nature we would point out that in civilised communities living in towns an enormous loss of valuable nitrogenous material is all the time taking place, inasmuch as all the waste products of the individuals of the community, instead of being returned to the land, are piped away through the sewers into the nearest river and so into the sea. This does not matter so very much in view of the fact that we have all the sources we have mentioned wherewith to replace the loss to the soil. But in the case of another element—phosphorus—the position is more serious. This is taken up from the soil by plants in the form of phosphates. When animals eat the plants they use such of the phosphorus as they require for the building up of those components of their tissues which contain this element. Phosphorus is of extreme importance in the formation of bone, and also in the formation of the constituents of the brain and nerves, but these are only the outstanding cases; there is not a cell in the body that does not require at least some of it. Any excess of phosphorus that is eaten over and above the requirements of the organism is got rid of partly in the urine and partly in the fæces, and in either case normally finds its way into the sewers and so finally out to sea. Now, while the similar loss of nitrogen in this way does not matter very much because we can now supply it from the air, the loss of phosphorus is one which is not so easy to make good. At present our only source of phosphorus consists of rocks that are composed entirely or in part of phosphates. These are mined and treated in various ways so that the phosphates become soluble and so available for the use of plants. But although there are enough

phosphate rocks in the world to last mankind for generations and generations, these supplies are not inexhaustible: and there will without doubt come a time when the conservation of this valuable element will have to be given more careful consideration than it receives at present. Even now attempts to utilise sewage for fertilising purposes are not absolutely unknown.

Some of the subjects discussed in this chapter have a bearing on a number of further problems that we ought at least to mention. For example, we have said nothing at all about the chemical structure of chlorophyll, although obviously, in view of its importance, this must be a matter of some interest. It is indeed of very great interest to find that the essential chemical units contained in chlorophyll are *porphyrins*—substances of the same class as those we found to be characteristic constituents of hemoglobin (page 183). When this first became known it suggested the idea that possibly during the course of the development of life the hemoglobin that we find in animals had somehow arisen from the chlorophyll of plants. But recently it has been shown that substances containing porphyrins are present in practically all protoplasm—even that which is not obviously coloured—so that it would probably be more correct to say that plants, and those animals that possess it in their hemoglobin, have derived their chlorophyll independently from the same raw materials that are found in all living matter.

These considerations also bear on the much-discussed question how life first appeared on the earth. "What," it has often been asked, "were the first living organisms like?" At first it would seem most natural to suppose that they were single naked cells—little bits of living slime—similar to the simplest animals we know to-day. But it has been pointed out that these simplest animals of to-day prey upon, and use as food, yet smaller organisms, mostly microscopic plants con-

taining chlorophyll. One of these simple animals would, if it appeared alone on the earth, inevitably die of starvation. It has, therefore, been suggested that the first organisms must have been tiny plant-like creatures, which by means of their chlorophyll would be able to build up food for themselves from simple materials absorbed from their surroundings. But still more recently it has been shown that some, at all events, of our simplest animals can dispense with solid food and can thrive on solutions of amino-acids, using these and other relatively simple substances as the raw materials of their life processes. And if the conditions were such that living protoplasm could come into existence at all, we have no difficulty in believing that amino-acids could also be present at the same time. So that perhaps, after all, the first organisms to inhabit the earth might have been more like animals than plants. But in this matter we can only conjecture. No one witnessed the birth of that original tiny speck of matter which was the first to possess the properties of what we call "life": no one was there to see how this amazing cycle first began.

But, as we have seen, the limited stocks of nitrogen, carbon, and other elements that we have on the earth *are* used first by one living thing and then by another; the very same materials may serve in turn as the basis of the life of a man, a germ, and a forest tree. And, as we have seen further, not only the actual substances they use but also the energy that these and other organisms expend is not "produced" by themselves but is in reality only "borrowed." The animal obtains energy by the breaking down in his body of the complex energy-yielding substances that have been built up by plants: but the plant has no way of producing for itself the energy necessary for the building up of these complicated materials. It absorbs the whole of this from the sunlight. So that when we use plant products for the purpose of obtaining

energy either inside or outside our bodies; when we burn the wood of our present-day forests or use coal, the fossilised remains of trees of bygone ages, we are simply recovering the energy of that light which was absorbed, perhaps, millions of years ago, by the green foliage those forests spread to the sun. Even when we use electric light, insofar as its power is generated by the burning of coal, we are benefiting by the wonderful property of chlorophyll to act as an accumulator of light energy.

We have discussed the whole question of these exchanges of matter and energy, both within the human body and outside it, in the cold, matter-of-fact language of scientific terminology, and have represented the complex interrelations between life and matter by mere lines on roughly drawn diagrams. But we have failed in conveying our intended meaning if the reader does not obtain more than mere scientific information from these crude and all-too-much simplified representations; unless he sees in them not only the order and economy of Nature but also some sort of expression of both the wonder and the pathos of that ceaseless cycle in which our own fleeting lives are embraced.

FURTHER READING

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1. Books containing accounts of Biochemical Topics for the general reader:

Crowther, J. G. *Short Stories in Science.* (London: Routledge).

Fox, H. M. *Blue Blood in Animals.* (London: Routledge).

Slosson, E. E. *Creative Chemistry.* (New York: Century).

2. Books supplying the background of Biology necessary for the serious study of Biochemistry:

Haldane, J. B. S. and J. S. Huxley. *Animal Biology.* (Oxford University Press).

Godwin, H. *Plant Biology.* (Cambridge University Press).

3. For the physiological basis:

Hill, A. V. *Living Machinery.* (New York: Harcourt).

Mottram, V. H. *Physiology.* (New York: Norton).

Ponder, E. *Essentials of General Physiology.* (New York: Longmans Green and Co.).

4. Easy introductions to Chemistry, the science that is fundamental to everything in Biochemistry:

Kendall, J. *At Home among the Atoms.* (London: Bell and Sons).

Muir, M. M. P. *The Story of the Wanderings of Atoms.* (London: Hodder and Stoughton).

5. Serious textbooks of Chemistry suitable as introductions to the study of Biochemistry:

Phillips. *Fundamentals of Organic and Biological Chemistry.* (New York: Appleton).

Lowy, A. and B. Harrow. *An Introduction to Organic Chemistry.* (New York: Wiley and Sons, Inc.).

Wade, J. (revised by H. Stephen). *Introduction to the Study of Organic Chemistry.* (London: Allen and Unwin Ltd.).

6. Standard textbooks of Biochemistry (in suggested order of reading):

Parsons, T. R. *Fundamentals of Biochemistry.* (Baltimore: Williams & Wilkins).

Cameron, A. T. *Textbook of Biochemistry.* (London: Churchill).

Mathews, A. P. *Physiological Chemistry.* (New York: William Wood).

Bodansky, M. *Introduction to Physiological Chemistry.* (New York: Wiley and Sons, Inc.).

Gortner, R. A. *Outlines of Biochemistry.* (New York: Wiley and Sons, Inc.).

Lloyd, D. J. *Chemistry of the Proteins.* (London: Churchill).

Pryde, J. *Recent Advances in Biochemistry.* (Philadelphia: Blakiston).

Also the series of Monographs on Biochemistry. (New York: Longmans Green and Co.).

For practical work:

Cole, S. W. *Practical Physiological Chemistry.* (Baltimore: Williams & Wilkins).

Bodansky, M. and M. S. Fay. *Laboratory Manual of Physiological Chemistry.* (New York: Wiley and Sons, Inc.).

Cameron, A. T. and F. D. White. *A Course in Practical Biochemistry*).

7. On Food and Nutrition:

Callow, A. B. *Food and Health.* (Oxford University Press).

Mottram, V. H. *Food and the Family.* (London: Nisbet and Co.).

McKillop, M. *Food Values: What They Are and How to Calculate Them.* (New York: Dutton and Co.).

Rose, M. S. *Feeding the Family.* (New York: Macmillan).

Holt, L. E. *Food, Health and Growth.* (New York: Macmillan).

Sherman, H. C. *Chemistry of Food and Nutrition.* (New York: Macmillan).

Lusk, G. *The Science of Nutrition.* (Philadelphia: Saunders).

Tables of food analyses:

Atwater, W. O. and Bryant, A. P. *The Chemical Composition*

of American Food Materials. Bulletin No. 28, U. S. Department of Agriculture, Washington.

Plimmer, R. H. A. *Analyses and Energy Values of Foods.* (London: H. M. Stationery Office).

For practical experiments on foods:

Clifford, W. M. and V. H. Mottram. *Properties of Food.* (London University Press).

Vitamins:

McCollum, E. V. and Simmonds, N. *The Newer Knowledge of Nutrition.* (New York: Macmillan).

Medical Research Council of Great Britain. Special report No. 38. On the present state of knowledge of accessory food factors (vitamins). (London: H. M. Stationery Office).

8. On muscular exercise:

Hill, A. V. *Muscular Activity.* (Baltimore: Williams & Wilkins).

Hill, A. V. *Muscular Movement in Man.* (New York: McGraw-Hill).

9. On blood:

Barcroft, J. *Hæmoglobin.* (Cambridge University Press).

10. For a glimpse at the philosophy of Biochemistry:

Needham, J. *Man a Machine.* (New York: Norton).

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